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BASIC RESEARCH
and its Application in the Field of
CLINICAL NUTRITION

By CHARLES GLEN KING, PH.D.*

AS A RESEARCH scientist, one must, of necessity, live very much in the realm of ideas or imagination; and as normal human beings, we develop our sense of direction for living and working very largely on the basis of ideals. In that ideal yet practical sense, we may define nutrition as the science of food and its relation to life and health. Then the goals toward which nutrition scientists work can be seen more clearly. First, they want to be able to identify and measure the concentration of all the useful ingredients in human and animal foods. Second, they want to know how each nutrient functions in living organisms, and how these functions interlink, one with another. Third, they want to know the quantitative relationships between nutrient intake and health on a life-span basis. And fourth, they sense an obligation to assist in the educational activities that will make their work effective in the community at large.

There are two basic reasons why it is urgent that we develop the science of nutrition. There is an unmistakable demand to produce enough food to protect the health of a rapidly growing world population. In so far as this basic requirement is not met, there will be needless and increasing human misery and social turmoil. If we study and attack the problem with sufficient vigor, there is a reasonable prospect that the peak of the population-versus-food struggle will be passed within two or three generations. The second situation is relatively new. Students of public health agree that medical progress in the years ahead is likely to result chiefly from discovering how to maintain a favorable chemical environment within the human body. The greatest research activity is already heading in the direction of warding off the degenerative diseases such as hardening of the arteries, high blood pressure, cancer, cirrhosis of the liver, diabetes, arthritis, obesity, tooth decay, premature births, glandular imbalance, and many forms of physiologically induced nervous instability.

NEW TERRITORY

One can scarcely miss noting the contributions that biochemists are making in cooperation with the medical profession in developing the science of nutrition. Among other reasons for this trend, clinical nutrition has moved rapidly from the older concept by which physicians were chiefly interested in curing and preventing deficiency diseases, such as scurvy and rickets, into a new zone of interest where the poor health condition cannot be

From the Nutrition Foundation, Chrysler Bldg., New York.

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identified with an obvious or recent cause. Hence, appraisals of nutriture or nutritional status are increasingly dependent upon microchemical analysis. Three examples will illustrate this point:

(1) Accurate methods are now available whereby a few drops of finger-tip blood taken during school health surveys can be analyzed for vitamin A, carotene, vitamin C, vitamin B_1, vitamin B_2, diphosphonucleotide (niacin index), hemoglobin, iron, serum protein, and the enzyme phosphatase.

(2) Physicists, chemists, and physicians at Harvard University and Massachusetts Institute of Technology are now working out detailed procedures for micro-analyses of blood samples to measure nearly all the trace mineral elements, so that medical research can be directed into this area more rapidly.

(3) Blood tests for specific immune bodies, hormones, complex fats, and specific enzymes furnish to the physician a record of metabolic trends that can be influenced by food intake, long before there are any external evidences of an impending break in health.

The Heart of the Situation

The growing importance of diseases associated with faulty metabolism compared with infectious diseases is emphasized when the principal causes of death are studied. In the United States, currently, only one of the five groups of diseases listed among the greatest causes of death can be classed as infectious (pneumonia and influenza). Heart and cardiovascular diseases are in first place, and cancer is in second position.

There is no room to doubt that a close relationship exists between food practices and this leading group of death-dealing diseases. An understanding of the chemical basis for the relationships, however, is just beginning to unfold.

Unquestionably, one of the most damaging practices is simply eating too much. An excessive intake of calories, alone, constitutes a major hazard to health, especially in the upper age bracket, but the prospect of warding off diseases associated with aging is made doubly hazardous when the high calorie foods are low in vitamins, minerals, and good quality protein.

In research on the degenerative diseases, one is impressed by the frequency with which abnormal fat deposits are characteristic of early lesions, long before there is evidence of a break in health. Hence, we feel confident that advances in knowledge of the manner in which fats are synthesized, distributed, and burned in the body will hasten the prevention and improve the treatment of these related diseases.

Among recent research contributions in this field, the following may be of especial interest.

Dr. C. H. Best and his associates at the University of Toronto found that young growing rats were so sensitive to choline deficiency that a diet from which this one nutrient was omitted, but otherwise complete in all respects, resulted in abnormal fat globules appearing in the livers and kidneys of the animals within twenty-four hours. When the deficiency was continued for three to five days, followed by return to a full diet, although growth and outwardly normal appearances continued, the initial injury was never fully corrected. When the animals reached maturity, instead of continuing as normal adults, they showed progressive degenerative changes in the arteries and heart and a gradual rise in blood pressure. The lesions were characteristic of those seen in human hardening of the arteries, high blood pressure, and enlargement of the heart. These observations were confirmed and extended by Dr. Philip Handler and his associates at Duke University.

This year Dr. Best, Dr. Hartroft, and their associates made a further discovery in noting that specialized cells adjacent to the kidney glomeruli were very sensitive to different levels of salt intake. Either too much or too little salt caused marked disturbances in the cells and they have postulated a new hormone function in the kidney cells that influences the adjustment of the adrenal cortical control of salt metabolism. A new lead is thus developing by which to find why and in what dgree low and high salt diets are so intimately related to the medical aspects of high blood pressure.

Cholesterol—Friend or Enemy

Nearly all investigators dealing with fatty livers, kidney disease, hardening of the arteries, and diabetes have been impressed by the frequency with which they find early and continuing deposits of cholesterol. The purely exploratory work of Rittenberg, Bloch, and others has been increasingly valuable in this area of medical research because they had shown that the animal body normally forms cholesterol in large quantities from acetate groups, which in turn are derived normally from carbohydrates and fatty acids. Hence, if one is attempting to suppress or control cholesterol concentration in the blood and to prevent its being deposited in excessive quantities in the tissues, the amount eaten in the form of meat, milk, and eggs is probably of secondary importance. There has been a tendency, especially since the publication of Dr. John Gofman's papers at the University of California, to attach too much importance to low cholesterol diets. Instead, the primary emphasis should be on low calorie diets of high nutritive quality. The mistaken conception of the origin of cholesterol has caused many physicians and writers to sponsor diets that are actually hazardous because of their poor nutritive quality.

A New Vitamin at Work

The work of Dr. F. Lipmann and others in discovering the role of pantothenic acid in forming co-enzyme A has been of notable value in correlating nutrition with both fatty diseases and the anemias. As outlined in the following scheme presented by Dr. Lipmann, co-enzyme A is a controlling catalyst regulating the metabolism of acetate groups. Studies of pantothenic acid deficiency in experimental animals have consistently shown a pattern of injury to the kidneys, adrenals, liver, and other glandular structures. Thus far, unfortunately, there has been extremely little research on the role of pantothenic acid in human metabolism or disease.

The stimulus to greater interest in this area of nutrition research is heightened by Dr. D. Shemin's recent work at Columbia University in discovering that co-enzyme A also serves as a controlling catalyst in the formation of protoporphyrin as a precursor of hemoglobin.

Cancer

The origin of human cancer is not known with enough certainty to evaluate the possible role of nutrition. Hence, one must be extremely careful not to imply too much from recent exploratory research with animals. In experimental animals, however, there are several instances where nutrition is a deciding factor in carcinogenesis. The Yale, Cornell and Wisconsin University groups, Memorial Hospital, and other highly qualified research laboratories have found that generous intakes of riboflavin (vitamin B_2) can, under specific conditions, play a decisive role in preventing cancer in several strains of rats. Careful experiments in another laboratory have shown that chronic choline deficiency, alone, can induce carcinogenesis in both rats and chickens. The low level of intake required to induce cancer, however, is much lower than one would encounter commonly in human experience. Of greater apparent significance are the many reports, especially those from the Michael Reese Hospital in Chicago, that an excess of calories and fat tends to encourage carcinogenesis. On the whole, despite many interesting leads, there is no convincing evidence, thus far, that dietary factors play an important role in causing human cancer. On the other hand, we have no reason to rule out nutritional imbalances as factors of importance in carcinogenesis. And from a practical point of view, we can be confident that continued advances in understanding the principles of cell function and nutrition will shorten the pathway to finding a solution to even this most complex problem.

Proteins

From the viewpoint of severe limitations in the quality and quantity of food supplies, there is much evidence to support the emphasis that has been placed on animal protein foods, such as milk, meat, eggs, and fish. Because of their relatively high cost, however, the task

of maintaining an adequate intake of these foods represents the most acute limitation in the total food problem. One's imagination is certainly taxed to the limit, for example, in suggesting a practical solution of the problem in India, China, South Africa, and sections of Latin America.

From a nutritional point of view, the animal protein foods can be resolved very largely in terms of essential amino acids and an abundant supply of vitamins in the B-complex. Within the last five years, advances in nutrition research have furnished much of the information that is essential to progress toward solving the protein problem—if it can be solved. Among these advances none is more important than the work of Professor W. C. Rose at the University of Illinois, who established for the first time a relatively complete picture of the adult human requirement for each individual amino acid.

In addition to the basic information supplied by Dr. Rose, perhaps the most significant discoveries regarding animal protein foods have dealt with the newer vitamins, especially folic acid and vitamin B_{12}. These two nutrients and choline are supplied in abundance by the animal protein foods. Their functions, in turn, have been rapidly interlinked with the functions and essential balances of other vitamins, amino acids, mineral elements, sugars, fats, and hormones, so that we have a greatly extended appreciation of what is meant by the old-fashioned terms "a good diet" and "good health." Folic acid was found to cure the tropical disease called sprue, and many cases of anemia found in temperate zones. Vitamin B_{12} furnishes protection against pernicious anemia and serves widely as a valuable growth factor.

In broader ways these discoveries contribute to the solution of practical problems. First, in areas where the need for protein foods is most acute, it is urgent to utilize plant protein foods to the greatest possible degree. Such a practice imposes an immediate hazard of failing to supply adequate sources of vitamin B_{12}. It is only when one can measure the individual amino acids and their associated vitamins in different foods, and then relate these quantities to the human requirement that one can plan production and educational programs with any sense of reliability. Furthermore, when supplied with definite information regarding amino acid and vitamin requirements, the agricultural geneticists can work to advantage in improving the quality of protein in such crops as corn, wheat, and legumes. This state of affairs offers certain obvious advantages over having to plan a series of field crop tests on the basis of life-span observations on the human population. An example is evident in the discovery by Dr. Rose that the human body can synthesize its entire requirement for histidine. In their present efforts to improve the protein quality of corn and beans, the geneticists have enough difficulty attempting to increase the content of three other amino acids, tryptophane, lysine, and methionine, without attempting to tie in a fourth one.

Balancing of Many Points

Dr. C. A. Elvehjem and his associates made a classical contribution in demonstrating a high degree of dietary interchangeability between niacin, the antipellagra vitamin, and tryptophane, one of the essential amino acids. The discovery simplified very greatly the entire problem of providing adequate diets in both human and animal feeding. The extent of known comparable interplay between other amino acids and vitamins has grown rapidly. For tryptophane, a second vitamin balance was discovered in the case of vitamin B_6. A currently used method of identifying vitamin B_6 deficiency in the human body is based upon administering a large amount of tryptophane and then measuring the degree of utilization or loss of the excess tryptophane.

Another example of a marked interdependence between amino acids and vitamins was discovered last year by Dr. W. D. Salmon and his associates in demonstrating that vitamin B_{12} is interchangeable with choline to an appreciable degree. A major quantitative interplay between choline and methionine had been recognized for several years. The need for choline, as commonly measured in standard experimental animals, can be varied as much

as 50 per cent by varying the intake of vitamin B_{12}. One might add that the requirement for vitamin B_{12} is also greatly conditioned by the intake of another vitamin in the B-complex, folic acid. In addition (as shown by Dr. R. R. Sealock, Dr. Paul Day, Dr. W. J. Darby, and others), the folic acid supply has a marked effect upon the requirement for vitamin C.

Findings of this kind give strong support to the view that in the development of practical plans for good nutrition, one must look upon the diet pattern as a whole and not be misled by overemphasis upon the supply of individual nutrients at specific levels. The primary educational measures should be based upon educating the public to consume liberal quantities of reliable protective foods. These generally fall into three critical groups, the animal protein foods, yellow and green leafy vegetables, and citrus fruits or tomatoes. Then caloric provision to maintain an ideal body weight can be furnished along with added supplies of essential nutrients by low-cost cereals and carbohydrates or fatty foods, according to circumstances.

Trace Minerals

Another rapidly moving area of nutrition research is represented by the trace mineral elements. Iodine deficiencies were formerly very widespread in America. The use of iodized salt has solved a large part but not all of the problem. In many sections of the world, however, distribution of iodine has scarcely been attempted. The Food and Agriculture Organization of the United Nations believes that iodine deficiency is one of the major world problems in public health.

Dr. N. S. Scrimshaw and his associates in the Central American countries, for example, have found several areas where the incidence of goiter among the Indians reaches at least as high as 80 per cent. Goiters were still regarded locally as a normal condition. Work on the problem is being initiated, and it appears that a solution is at hand in the use of iodate salts instead of iodides. The iodides are too unstable for use in crude salt supplies.

Tooth Decay Not Necessary

Much closer to the research atmosphere is the attempt to provide sufficient fluoride to the human population to accomplish optimum protection against tooth decay. Approximately 150 cities in the United States have initiated plans to furnish fluoride to the entire community at a level of approximately one-part-per-million in the public water supply. The practice of fluoridation does not seem to have developed as rapidly in other countries, but there is no doubt that extension of fluoridation will continue at a rapid pace in American communities. Fluoridation alone should not be expected to completely solve the dental caries problem, however, because other nutrients make important contributions to caries-resistant teeth. There is still an urgent need to educate the public toward decreasing tooth decay by means of a diet that is adequate in all respects. The clinical observations of Dr. Toverud and his associates in western Europe, Dr. Sognnaes and his associates at Harvard University, together with the studies of Dr. Elvehjem and Dr. Phillips at the University of Wisconsin, have shown that good nutrition can play a dominant role in preventing tooth decay. Their work is essentially new also in pointing toward the importance of good diets during gestation and very early growth, in contrast to earlier emphasis upon dietary effects after the teeth were erupted. Monkeys and rats reared on a composite diet of natural foods until about half-grown, and then placed upon conventional diets comparable to our human food supply showed practically no dental caries even with a large amount of sugar in the diet. On the other hand, the same types of animals reared through the complete reproductive cycle of gestation, lactation, and growth on partly purified diets showed a high incidence of dental caries.

Again, Balance

Another interesting area of trace element research deals with the interrelationships of the heavy metals. It has long been known that copper must be supplied in about one-

tenth the amount of iron to make possible the utilization of iron in forming hemoglobin and the iron-containing enzymes. The manner in which copper functions in animals is almost a complete mystery, although its presence in several plant enzymes has been well established.

In some of the Atlantic seacoast areas, as in Florida, it is a common practice to add molybdenum with other fertilizer ingredients. Cattle grazing in some areas developed a disease characterized by rapid loss of weight, diarrhea, and anemia. It was then discovered that the condition could be cured by administering salts of copper, although the forage crops appeared to have a normal copper content. Later they found that some of the forage plants had accumulated too much molybdenum, and the molybdenum had created an increased demand for copper. Additional copper then served to reëstablish a balance and approximately normal health. More recently they have found that cobalt can serve in a similar way. The chemical basis for these relationships is not at all evident, but at least there exists this quantitative interdependence between iron, copper, molybdenum, and cobalt. Even before worrying about the effect upon animals, the farmer finds that a slight change in acid-base balance of the soil can greatly alter the availability to plants, of iron, copper, molybdenum, manganese, and cobalt.

The soil bacteria use cobalt in a great variety of ways, including the formation of a series of true and pseudo forms of vitamin B_{12}. The relation of these nutrients to antibiotics is scarcely understood at all, except in empirical observations based on feeding to see what happens. Nevertheless, feeding antibiotics, such as penicillin, aureomycin, and terramycin, is an established practice in raising chickens, turkeys, and pigs. Under supervision, the antibiotics are being fed to children, with reasonably favorable results.

Conclusion

Exploratory research in the science of nutrition, followed by diligent efforts to apply the findings in terms of medicine, agriculture, and education of the public, represents one of the most promising areas of graduate, professional study. And in addition to the scientific aspects of such work, the social and economic contributions inherent in each advance offer a reasonable basis for laying foundations under the kind of a civilization that our children may want to build.

Resumen

Estudios básicos y su aplicación en el campo de la nutrición

El autor pasa en revista varios importantes adelantos recientes en el campo de la nutrición que han resultado de investigaciones en les ciencias básicas, particularmente en la bioquimia. El interés, en lugar de concentrarse en las enfermedades deficitarias específicas—tales como la raquitis y el escorbuto—se dirige ahora hacia las enfermedades degenerativas. La producción retardada de la hipertensión consecutivamente a una deficiencia pasajera de colina en ratas no es más que un solo ejemplo. El énfasis se ha trasladado del colesterol exógeno a aquello endógeno como factor en la génesis de la arteriosclerosis.

Otras observaciones se describen, tales como los efectos de las vitaminas en el cáncer experimental, el papel de los oligoelementos, los factores que contribuyen al decaer de los dientes, las relaciones entre la triptofana, la vitamina B_6 y la niacina, o entre la cianocobalamina (B_{12}) y los ácidos fólico y ascórbico. El trabajo de Rose y otros en definir más claramente nuestros requerimientos nutritivos específicos se nota. Este conocimiento permitirá a los pueblos y naciones un mejor planear y ajustar de sus responsabilidades alimenticias. Las investigaciones en las ciencias básicas se aplican prontamente al campo de la nutrición: medicina, agricultura, y educación pública. Este esfuerzo en traducir los hallazgos de la experimentación en términos prácticos constituye uno de los campos más prometedores para el estudio graduado y professional.

Dietary Treatment of HYPERTENSION

By IRVINE H. PAGE, M.D. AND A. C. CORCORAN, M.D.

The Patient ought likewise to be considered, whether he is able to hold out with the prescribed diet . . . for if the diet is not sufficient, the patient will grow too faint, and be overcome . . .

—Hippocrates, Aphorism IX

The best doctors in the world are Doctor Diet, Doctor Quiet, and Doctor Merryman.

—Dean Swift, after the Regimen Sanitatis of Salerno

THESE AND many other more ancient and extensive quotations could be adduced in support of the fact that treatment by diet is one of the oldest and most difficult modes of therapy. It is old because the shrouded empiricism which gave birth to primitive medicine soon determined that diet had an influence on disease. Physicians ever since have tried to construct adequate scientific bases for their several diets. It is difficult because whatever the justification turned out to be, the therapist has always been forced into an awareness of the importance and variety of the patient's reactions to the regime.

The natural inclinations of many persons dispose them to the concept that what they eat determines what and how they are. From these, in all ages, have been recruited the food faddists and their dubiously scientific guides. Others, more cynical or hedonistic, rationalize their desire for variety in viands by the assumption that any form of dietotherapy is more or less inherently dishonest as well as distasteful. The former group can with difficulty be restrained from diets which may do them harm; the latter can hardly be induced to diets which will certainly do them good.

Certain forms of dietotherapy are now of proved and almost universally admitted value in various forms of cardiovascular-renal disease. Thus, no one doubts the value of caloric restriction in the obese; it is recognized that the protein loss associated with the nephrotic syndrome can be countered, perhaps not too effectively, by protein supplements. In the presence of renal failure, provision of high caloric, low protein diets seems to prolong life and well-being by staving off the onset of uremia. Similarly accepted is the value of restriction of sodium chloride intake in patients suffering from congestive heart failure or the nephrotic syndrome. But the value of diet in the treatment of essential hypertension as such, in contrast to its use in the treatment of complications of this disease, has not a comparable acceptance, neither as to the fact nor as to the form the diet should take.

This is unfortunate, because dietotherapy of hypertension is as old as our knowledge of its existence. French and German clinicians at the turn of the century made claims for the restriction of salt and especially of chloride intake, basing these on clinical impressions unsatisfactorily evidenced and uncritically sup-

From the Research Division of the Cleveland Clinic Foundation, and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

ported. In varying degree because of the nature of these pretensions, the prevailing lack of interest in the treatment of hypertension, and the desultory knowledge of its mechanisms and natural history, these low salt diets made headway only in the most obscure and shady quarters. However, in the early 1920's Allen and Sherrill vigorously advocated severe salt restriction in patients with hypertension. Their arguments were supported by clinical records more convincing than any previously available. Volhard added his authoritative opinion to their evidence.

Some few attempted to confirm these claims by clinical experiments which were generally unsuccessful. This lack of success can now be seen to have stemmed from two causes: first, the prevalent emphasis on chloride rather than sodium and, second, the impossibility of providing a diet which would contain less than 1 Gm. sodium in one day's intake, while maintaining, as was then considered necessary for well-being, an intake of 1 Gm. per kilo body weight of protein per day. Consequently, clinicians in general remained unconvinced; and, faddists apart, the low sodium dietotherapy of hypertension lapsed for still another twenty years.

During this time knowledge of the mechanisms and course of hypertensive disease increased greatly; methods of clinical study were improved, and observations in animals with experimental hypertension began to supplement those made in patients. In particular, Selye's[1] production of hypertension and hypertensive disease in rats by the administration of sodium and desoxycorticosterone, drew attention to the possibility that sodium might be concerned in the hypertension of human beings.

The revival of low salt dietotherapy by Grollman, Harrison and co-workers[2] resolved two major difficulties: first, the emphasis was properly placed on sodium rather than chloride; and second, the restriction of sodium intake was more drastic than any previously maintained over long periods. The restriction was obtained by providing dialyzed milk as part of the protein supplement.

The Kempner rice diet[3] got under way at about the same time. To those who think only in terms of fluffy white kernels, the name is more attractive than the monotonous fact; however, when prescribed with authority and enthusiasm, when undertaken in the team spirit of the rice-houses, and when followed by the faintly masochistic, the rice diet admittedly yields some startling clinical results. Most investigators were dubiously impressed by the theoretical basis first suggested for it. This assumption was that animal protein yields toxic metabolites which, in the presence of diseased renal tissues and enzyme systems, cannot be detoxified and are vasopressor; the products of rice protein metabolism were considered non-toxic, so that the rice diet was advocated as a means of compensating for a hypothetical renal metabolic dysfunction. Little emphasis was placed on the fact that the diet provides less than 200 mg. of sodium in one day's intake and that, in this respect, it corresponds to the diet used by Grollman and Harrison.

Experimental Evidence

A. Animals: Normal and Hypertensive. As noted above, the administration of sodium as sodium chloride, or in other forms, to uninephrectomized, but otherwise normal rats, during treatment with desoxycorticosterone acetate (DCA) elicits hypertension and hypertensive vascular disease[1] and this rather reproducibly.[4] Similarly, establishment of a positive sodium store by administration of hypertonic (2 per cent) sodium chloride as drink results in hypertension,[5] although not in as severe a form as when sodium retention is forced by giving DCA. The action of DCA is apparently renal, since placing a DCA hypertensive rat in parabiosis decreases arterial pressure, while separation from parabiosis or removal of the remaining kidney of the uninephrectomized DCA-treated animal restores the hypertension.[6] A criticism of experiments in rats arises from the responsiveness of arterial pressure in this species; thus, whereas variations in dietary protein intake have little or no effect on arterial pressure in human beings, the blood pressure of rats varies to some extent with protein intake.

Normal and/or uninephrectomized dogs seem to excrete excess sodium with much greater facility than rats, so that wide variations in sodium intake do not influence arterial pressure in dogs; even when sodium retention is forced by giving DCA, dogs show little or no increase in arterial pressure. Dogs differ in this respect substantially from rats and, as it seems, also from man, who, particularly in the presence of renal or adrenal insufficiency, is prone to DCA-salt hypertension. An experiment has been widely quoted in which it seemed that the rice diet resulted in decreased pressure in dogs in which renal hypertension had been caused by injection of streptococci; however the method of producing hypertension is bizarre, the course of the hypertension uncertain, and the data are inconclusive.

B. Human Beings: Normotensive. Wide variations of sodium intake have little if any influence on arterial pressure levels of normal human beings. Some patients with hypertension tend to retain administered sodium during subsequent sodium deprivation to a greater degree than most normal people;[7] it has been predicted that those normotensive people who show an increased tendency to sodium retention are therefore prehypertensive.[8] But the demonstration is far from complete; perhaps the first aim of such studies should be to delimit a category of sodium-retaining and sodium-responsive hypertensive patients. Observation in normotensive patients under treatment with ACTH and cortisone suggests that these agents may elicit increases in arterial pressure when sodium intake is normal or excessive, but that such hypertension is usually prevented by sodium restriction; concurrent renal damage is an uncontrolled susceptibility factor in many of these studies. Perhaps the most clean-cut evidence of adrenal cortical-sodium influences on arterial pressure regulation stem from experiments which show that restriction of sodium enhances the depressor effect of injections of tetraethylammonium chloride (TEAC) in normal subjects and decreases the tendency of the "TEAC-floor" to rise during administration of ACTH or cortisone.[9,10]

Thus, in brief, experiments in normal and hypertensive animals and in normotensive human beings do not resolve the problem of sodium and hypertension. Sodium has a definite influence on hypertension in rats; it has little influence on arterial pressure in dogs; it has suggestive influences on arterial pressure responses to TEAC in normotensive human beings; the issue is clouded in some degree by variations in adrenal cortical and renal excretory mechanisms as between these species. In particular, the mechanism by which sodium retention or depletion influences arterial pressure in a responsive subject such as the rat has not been elucidated; terms such as "overhydration," expansion or contraction of extracellular or intracellular fluid volume or composition merely fog the issue until it can be shown that some specific change in one of these categories has a direct influence on arterial pressure and vascular reactivity.

C. Hypertensive Human Beings. In the absence of other conclusive evidence, we must therefore deal, more or less empirically, with clinical experiments in hypertensive human beings.

The essential preliminaries to such experiments must be briefly noted. These concern above all the need for properly controlled observations. Lack of these and reliance on "clinical impressions" have been the major factors in retarding the proper application of low sodium dietotherapy. Admittedly no one, neither the patient nor physician, enjoys a term of delay and observation before the application of what may or may not be a remedial agent. However, this seems to be unavoidable in any investigation. We deal with a disease in which we can observe (a) arterial pressure and (b) evidences of hypertensive cardiovascular disease (ECG, heart diameter, renal function). Arterial pressure is notoriously variable. The evidences of hypertensive cardiovascular disease sometimes remit unexpectedly. Consequently, there seems to be no substitute for an interval of at least several weeks observation during which these measurements are made and repeated. The aim is to arrive at an unequivocally steady state.

Some patients reach this in two or three weeks, others may require months, and some never arrive. As concerns arterial pressure, the plotting of daily measurements demonstrates a range; it does not prove a mean. We have for years averaged the fourteen morning and evening pressures obtained each week and, as shown in Figure 1, the plot thus obtained is amazingly steady, and significant deviations from the steady state are readily visible. The need for such a control necessarily slows the process of experimentation; but without it the experiments are fruitless and carry no conviction. The clinical investigator should remember the cardinal principle that two or three valid experiments are worth many hundred observations in which the aim has been to force conviction by the mere multiplication of observations. As concerns specifically the problem of low sodium dietotherapy, it is obvious that the attainment of a steady state presupposes that, during the control period, the sodium intake should be maintained at known and relatively constant levels and pref-

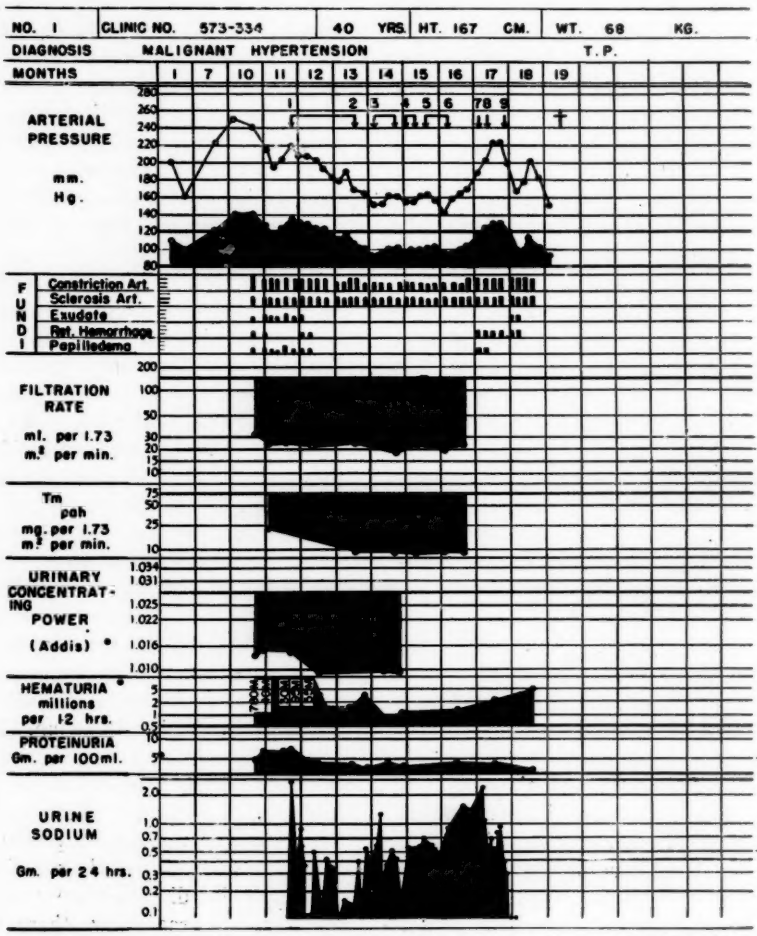

Fig. 1. Course of a patient treated by rice diet: (1) a supplement of 0.5 Gm. NaCl daily, (2) required because of hyponatremia, supplements of sodium-free proteins, and amino acids[3,4,5] and one such containing sodium (1.6 Gm. daily). The latter resulted in rapid deterioration of renal function. Progress to fatal uremia was not prevented by various low-sodium regimen (From *Circulation* 3:1, 1951.)[7,8,9]

erably at the levels which obtain in the patient's or the public's normal diet.

After such control periods, diets which are low in sodium (about 0.2 Gm. daily) but which provide a customary protein ration have been shown to (a) decrease arterial pressure in a minority of hypertensive patients and (b) ameliorate the evidences of hypertensive vascular disease in the pressure-responsive group.[11,12,13,14,15] It is essential to these demonstrations that during the control period the patient receive a 0.2 Gm. sodium diet supplemented by enteric-coated sodium chloride tablets; that during the period of dietary test the sodium chloride be replaced by placebo tablets of identical appearance; and that the sodium chloride dosage be resumed in a post-test control period. And it goes without saying, or should, that urinary sodium should be frequently measured during each of these phases. To be considered "sodium-responsive," the patient must demonstrate an unequivocal decrease in arterial pressure during the test period, with a rise during the post-test control to approximately pre-test control levels.

Similarly tested, the rice diet is shown to result in a decrease of arterial pressure and clinical remission in some patients;[12,15] the effect of the rice diet is abolished by sodium alimentation, but is not altered by provision of sodium-free protein or fat. The studies with both diets emphasize that (a) the level of sodium restriction required is very low—certainly less than 0.5 and probably about 0.2 Gm. daily, and that (b) the effect of the deprivation may not be apparent for several (perhaps 6) weeks and that improvement may continue after this time.

It is an unfortunate but recurrent aspect of medical science generally that the life story of a problem so often consists in: (1) the making of claims on inadequate evidence; (2) the bolstering of these by enthusiastic or misguided coat-tail riders on grounds equally or perhaps even more specious; (3) a tedious, necessary revision of the experimental plan; and (4) the presentation of adequate data. In a more orderly world, the last should be first, and the first, last. Such has not been the case with low sodium dietotherapy.[16]

Clinical Problems

If now we accept the fact that restriction of sodium intake to a level of about 0.2 Gm. daily remits the progress of hypertension and hypertensive vascular disease in a minority of patients with essential hypertension, and this usually over a period of several weeks, what problems remain?

The first is that of selection of patients. No one voluntarily consumes such a diet (Job vi, 6). No one appreciates being placed on it ineffectively. Unfortunately, the proof of the pudding is still the eating of a low sodium diet. High hopes have been entertained for selections based on: (a) the clinical impression of a Cushing syndrome, *forme fruste;* (b) the sodium content of saliva and sweat; (c) the ranges of urinary formaldehydogenic corticoids; and (d) the tendency to sodium conservation under conditions of depletion. None of these is substantiated as yet. A possible alternative is to force the issue by rapid depletion of sodium,[17] as by administration of mercurial diuretics during low sodium dietotherapy, hoping thereby to demonstrate the effect or lack of it in days rather than weeks. Here again the issue is not satisfactorily resolved. Our impression is that the process associated with sodium restriction which sometimes ameliorates hypertension develops slowly, so that perhaps it cannot be forced. This impression is perhaps restated in the hypothesis[15] that "the clinical benefit of the diet (in this instance the rice diet) did not appear to be associated with depletion, but, on the contrary, with successful adaptation" and that "the therapeutic effect is a consequence of the steady state adaptive response to limitation of sodium intake."

The next problem is that posed above by Hippocrates, "whether he is able to hold out with the prescribed diet." This failure to hold out may be psychologically, socially, or functionally determined. The psychological determinant is an attitude on the patient's part that, no matter what happens, he wants whatever is coming to him of the real or fancied

goods of this world, salt included. A certain tinge of masochism or of gut orientation of the unconscious is perhaps helpful here; a definitely cynical or hedonistic point of view is wholly destructive. A hedonism not too deeply rooted can often be overcome by persuasion, enthusiasm, or by threats—although the latter should not be lightly undertaken. The social determinants are just as difficult; many people as part of their livelihood "eat out" and, with the best of intentions and good will, cannot force the serving of foods of the desired low sodium content. Fortunately, low sodium foods and diets are becoming increasingly available in many centers. But there will probably always remain those who cannot get them, or if they could get them, cannot pay the extra costs.

What is noted as the functional determinant is the inability of some patients with moderately or far-advanced renal disease to retain sodium. The result is a heightened susceptibility to hyponatremia and the "low salt syndrome,"[18] with the attendant risks of complications to which patients with advanced cardiovascular disease are susceptible. The danger is naturally greater in hot weather or among people who work in high environmental temperatures. In many of these, a point of balance can be struck between the irreducible minimum of renal sodium excretion, which may be as much as 1 or 2 grams daily, and the amount provided for in the diet or as a supplement of enteric-coated sodium chloride. Properly managed, some patients can "hold out" while retaining the advantages of the diet. But the point of balance must be carefully determined, preserving the patient from listlessness, anorexia, nausea, and eventual coma.

In this connection, the rice diet has performed several useful functions: (1) it has provided a practical low-sodium diet, so restricted in its content as to allow the least possible room for play of the patient's imagination or ignorance; (2) it has demonstrated the possibility of effective survival on a diet of low protein content and on a diet which is very low in fat; and (3) it has also shown the harmlessness of rapid weight loss. Under the limited activity of the hospital, patients on this diet usually establish a minimum weight and nitrogen balance in 3 to 6 months. With the need for forced and violent physical activity will come the need for more protein and calories if this state is to be maintained.

The choice of diet is necessarily individualized. The patient with uncomplicated established essential hypertension who shows evidences of slowly advances vascular disease has the choice of (a) the rice diet or (b) the 0.2 Gm. sodium diet supplemented by salt-poor milk powder (Lonalac). The rice diet recommends itself to those naturally disposed to diets or intellectually unable to make the decisions needed for adequate sodium control as long as there are many possibilities of selection; it is also advisable in the obese, and particularly the obese with heart failure, or in any with azotemia. The more attractive drastic low sodium diets, such as described by the American Heart Association manual or in that of Dr. Thurman B. Rice, will be more appetizing, practical, and sustaining. It is too bad that the emphasis on rice as such detracts from the possibilities of such low sodium foods as baked potatoes, shredded wheat, and other palatable variations on the cereal theme. Other *adequately* certified low sodium foods (bread, fish, and meat) are now widely obtainable, although sometimes inordinately expensive. Among these, let the buyer beware.

Extra-dietary sources of sodium (stomachics, tooth paste, water softeners, city water, dentifrice) should be looked for as the patient starts on the regimen. The adequacy of dietary control can be determined as the weeks go on or by bi-weekly checks of urinary sodium content. Chloride analyses, especially when a chloride-rich "salt substitute" is used, do not substitute for determination of sodium; such determinations are now widely available. As concerns the salt substitutes, none is really satisfactory; they are useful palliatives in the first weeks of low sodium dietotherapy for some people who find out how they like best to use them; but, as time goes on, most patients lose their taste for salty foods and with it their dependence on the so-called "substitute." Lithium chloride is an excellent substitute from the aspect of taste, but it is dangerously

toxic under conditions of drastic sodium restriction;[21] the others are harmless, except as their potassium content is dangerous in the presence of renal failure and oliguria.

Much has been made of the possibility of substituting cation-exchange resins for sodium restriction in the treatment of hypertension. These agents are now available in forms which, in the absence of renal failure, are relatively harmless and do subtract from the body amounts of sodium which vary with the dietary intake. Unfortunately, they act by chemical partition; except under conditions of very severe sodium restriction, they always leave enough sodium behind to interfere with the effect of sodium restriction on hypertension. Fortunately, less restriction seems to control the nephrotic syndrome, congestive failure, and cirrhosis (Fig. 2).

The status of low sodium dietotherapy in the syndrome of malignant hypertension is more vexed than in patients whose disease is not rapidly advancing. The rate of progress of malignant hypertension is sometimes so swift that the patients do not have time to benefit from the diet before their disease has

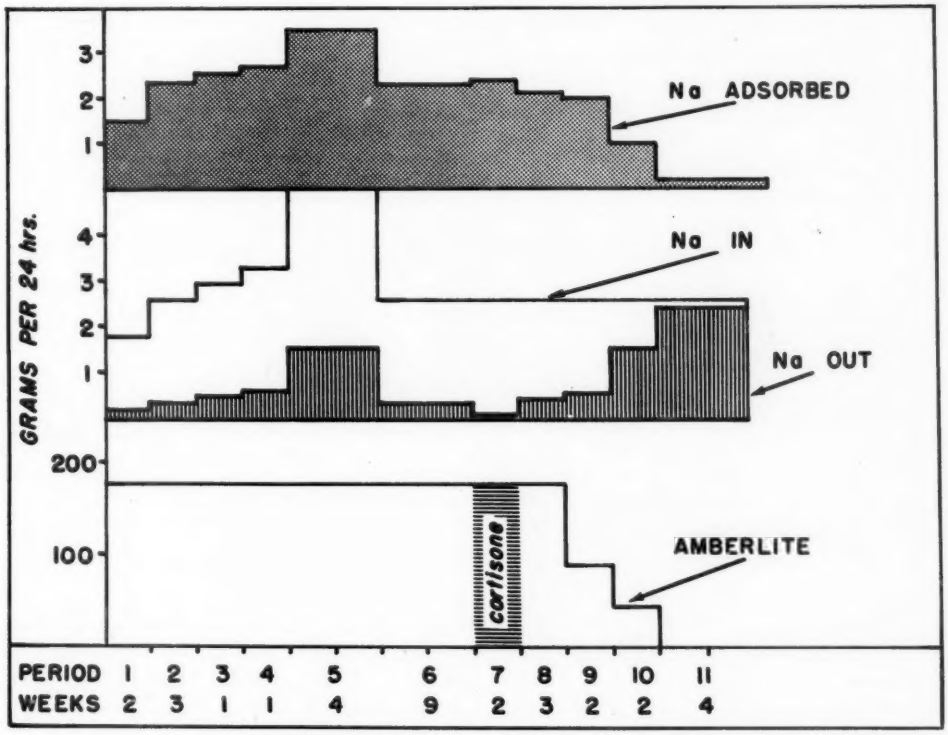

Fig. 2. Effect of an ion-adsorbing resin (Resodec®, Smith, Kline & French) on urinary sodium output (Na out) averaged over varying periods of sodium intake (Na in) and at different levels of resin dosage (Amberlite®) ranging from 180 to 45 Gm. daily. The amount of sodium adsorbed by the resin is estimated as the difference between Na intake and Na urinary output; validity of the estimate is established by the approximation of these values in the last period when no resin was given. In this patient, the mean adsorption of sodium from a diet containing 2.7 Gm. daily on a usually tolerable dosage of resin (45 Gm. daily) only slightly exceeded 1 Gm.; doubling the dose of resin brought adsorption to nearly 2 Gm., a level of restriction still insufficient in this patient to establish the decrease of arterial pressure previously observed in him when placed on diets containing 0.2 Gm. sodium daily (Fig. 1).

destroyed them. In some patients the condition is less rapidly progressive and some of these improve remarkably (Fig. 3). But, in general, the tendency is to use other more promptly effective measures in this condition, alone or in combination with the diet.

Much has been made of the effects of low sodium dietotherapy on renal function; it is variously stated to improve, remain constant, or decrease. Our own experience is that, congestive failure apart, it does not definitely improve; with 0.2 Gm. protein-adequate diets it usually remains constant in all particulars; with the rice diet there is usually a decrease in renal blood and plasma flow, glomerular filtration rate, and tubular secretory capacity for substances such as PAH, although the decrease is not clinically prejudicial.[12,13,19] Of course, with the onset of hyponatremia, and its attendant oligemia and vascular collapse, the deterioration of renal function is rapid and severe.

Lastly, the problem of what is politely called "combined" or rudely characterized as "shot-gun" therapy, viz., concurrence of low sodium dietotherapy with other measures. It has been claimed but not proved that sympathectomy, when otherwise ineffective, sometimes benefits the patient by making his hypertension responsive to sodium restriction. We have shown in one patient a statistically significant effect of the combination of low sodium diet with pyrogen treatment. The combination of low sodium diet and "Apresoline" (hydrazino-phthalazine, C 5968) is not in our hands usually more effective than either the diet or the drug alone. What may be a synergism and a justification for combined treatment occurs with hexamethonium; this drug is presumed to act, like TEAC, by causing partial blockade of sympathetic ganglia. As noted above, the depressor effect of TEAC is enhanced by sodium restriction. It is not, therefore, surprising that Smirk's[20] experience and our unpublished observations suggest that hexamethonium is more effective during sodium restriction. It is not clear whether or not sodium restriction also delays the onset of "tolerance" to this drug. While the effects seem now to be synergistic rather than additive, this is not proved. Until it is, we recall that claims for empirical "synergisms" are very often the unfounded rationalizations brought forward to justify uncontrolled experimentation.

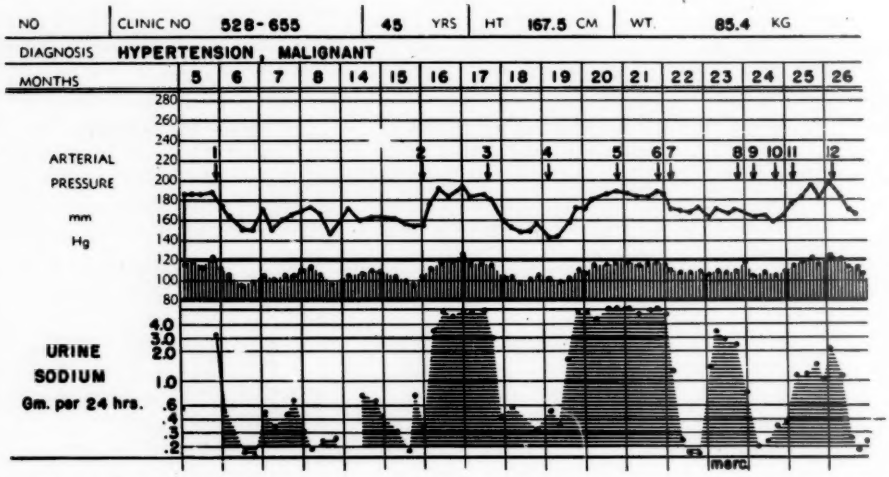

Fig. 3. Relation of arterial pressure and urinary sodium on Lonalac ® diet. Periods charted are (1) on 0.2 Gm. sodium; (2) the same plus 18 Gm. sodium chloride; (3) the 0.2 Gm. diet only; (4) as in 2; (5) the same with ineffective ion-absorbing resin; (6) as in (1) and (3); (7–12) reflect effects of varying dosages of sodium chloride and ion-adsorbing resins. (From *Circulation* 3:1, 1951)

Summary

In spite of the belated application of scientific method to the study of low sodium dietotherapy in hypertension, it has now been shown that a minority of patients with established essential hypertension respond favorably to diets containing about 0.2 Gm. sodium in each day's intake. In such diets, protein intake may be sustained by use of sodium-poor milk powder or similar preparations, or it may be sacrificed as in the rice diet. The choice is determined by the needs and possibilities of the patient.

Psychological, social and economic, as well as functional factors powerfully influence the success or applicability of low sodium dietotherapy. Lacking other proven means of speedy selection, the "proof of the pudding is in the eating" of a low sodium diet for at least 6 weeks, during which time the adequacy of sodium restriction is ensured by frequent checks of urinary sodium output. The cation-exchange resins are not as yet adequate substitutes for rigid sodium restriction in the treatment of hypertension.

The combination of low sodium dietotherapy with other modes of treatment is generally deprecated unless it can be shown that the combined treatments have advantageously additive or synergistic effects. To date, the most definitely advantageous combination is the special case of combined hexamethonium, low sodium dietotherapy.

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Resumen

Tratamiento dietético de la hipertensión

A pesar de la aplicación tardía del método científico al estudio de la dietoterapía de la hipertensión por el régimen pobre en sodio, queda demostrado que una minoría de enfermos afectados de hipertensión arterial esencial establecida responden favorablemente a dietas que contienen unos 0.2 g. de sodio diarios. En tales dietas, la ingestión de proteínas o puede ser mantenida por el uso de polvo de leche pobre en sodio o de semejantes preparados, o sacrificada, como en la dieta de arroz. La elección se determinará por las necesidades y posibilidades del enfermo.

Factores psicológicos, sociales y económicos, así como funcionales, ejercen una influencia poderosa sobre el éxito o aplicabilidad de la terapéutica por el régimen pobre en sodio. A falta de otros métodos seguros para conseguir la elección rápida, la prueba del régimen pobre en sodio consiste en observarlo durante al menos 6 semanas, período en el que la suficiencia de la restricción sódica se asegura por análisis frecuentes de la excreción urinaria de sodio. Las resinas de cambio de cationes aún no constituyen substitutos adecuados a una restricción rígida de sodio en la terapéutica de la hipertensión.

La asociación del régimen pobre en sodio con otros métodos de tratamiento se desaprueba generalmente, a menos que se pueda demostrar que el tratamiento asociado produce efectos aditivos o sinérgicos ventajosos. Hasta ahora, la combinación terapéutica más efectiva la constituye el caso especial del régimen pobre en sodio y hexametonio asociados.

GROWTH FAILURE *in School Children*

Further Studies of

VITAMIN B_{12} DIETARY SUPPLEMENTS

By NORMAN C. WETZEL, M.D., HOWARD H. HOPWOOD, M.D., MANUEL E. KUECHLE, M.A., AND ROBERT M. GRUENINGER, PH.D.

THE FIRST clinical investigation of vitamin B_{12} dietary supplements for children with simple growth failure was carried out at the Fresh Air Camp of Cleveland in 1949,[1] and that report, for brevity, may be referred to as the FAC Pilot Study. Significantly positive effects on growth along with better appetite and general clinical improvement were found, not in a series of normal children who had been growing satisfactorily, but rather in 5 of a small group of 11 children who had been under regular institutional care for growth failure, and who had, in addition, received daily oral supplements of crystalline vitamin B_{12}.

Not only were the responses to B_{12} supplementation—measured as differences between before and after rates of gain—in each of those 5 subjects quite substantial, but they were highly significant in the statistical sense, as well. Actually, the probability, p, that the results might have occurred by chance proved to be less than 0.001 in 4 of the 5 subjects (and a value of $t = 8.96$ was even obtained for one child [Case 5] for whom a particularly long and stable set of prior data had been available). Assurances of such degree are rarely expected in ordinary clinical work, and, when attained, they convey unmistakable meaning. In the FAC study they had, in fact, a double significance, for they indicated not only that vitamin B_{12} has a definite growth effect in children with growth failure, but also that child growth itself, when properly followed, is much less erratic in its trends and behavior than many are inclined to believe.

The FAC observations were made at a time when B_{12} was dispensed in ampoule form only,

From The Children's Fresh Air Camp and Hospital of Cleveland; the Dept. of School Health Services, the Dept. of Health and Physical Education, Shaker Heights Public Schools; and from the Dept. of Physical Education, Western Reserve University, Cleveland, Ohio.

The preliminary phases of this work connected with Grid installation and survey were carried out with support by grants-in-aid from the Louis D. Beaumont Trust and from the Elisabeth Severance Prentiss Foundation. The follow-up Nutrition Study Program, devoted more particularly to the investigation of dietary supplements, was supported by grants-in-aid from Merck & Co., Inc., Rahway, N. J., The Wm. S. Merrell Company, Cincinnati, Ohio, and Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

and when hypodermic injection was the regular mode of administration, largely because pernicious anemia was the only known clinical indication for its use. They happened also to have been made at the time when a re-survey of the prevalence and distribution of simple growth failure in the public schools of Shaker Heights, Ohio, had been completed under supervision of the Medical and Health Departments. Just as others which preceded it, the survey dealt with precisely the same clinical entity that had been under observation in the FAC vitamin B_{12} study. The survey findings revealed what had long been known to the Medical Department and what has more recently been confirmed by Deisher and Bryan[2] and by Clemmons and Williams,[3] namely, that simple growth failure in the school population continued to be as great a challenge as ever, individually as well as from the standpoint of preventive group health work. Thus, the desirability of arranging for a critical study of vitamin B_{12} dietary supplements in conjunction with a School Nutrition Program, similar to extra-milk or hot-lunch projects, was naturally suggested by the FAC results, and the suggestion itself was clearly supported by a number of other important and practical considerations that deserve brief mention.

In the first place, simple growth failure even among children of high-income areas had been, and continues to be, on the increase. Poor or faulty nutrition may, or may not, happen to be involved as a primary cause of growth failure in such areas, but good nutrition, on the other hand, is always a necessary part of recovery from growth failure and hence of any efforts to promote recovery. Moreover, growth failure left to itself tends to get worse, and institutionalization is certainly not the only nor, in most instances, a practical solution. Therefore, if growth failure is to be handled successfully it must be taken care of "on location"—which is to say, in the very environment and under the very conditions that have allowed it to develop, namely, in the ebb and flow of a child's home and school life.

There was, however, no evidence available at the time to show whether B_{12} supplements are as effective outside of an institution as they had proved to be for the children under Fresh Air Camp care. Indeed, since no "out-of-FAC-comparisons or controls" had been provided, the original findings, strictly speaking, were valid only for children living in an institution and not for children living at home.* Yet, knowledge on how effective B_{12} supplements are for "growth failures" in the natural environment of their own home life is just the kind of information which physicians and pediatricians require when considering recommendations for children with simple growth failure whom they encounter in practice. Thus, group studies, properly organized and carried out under suitable auspices, could add materially to individual case reports; and, by proper design, they could especially lead to more precise information on the extent to which other factors influence outcome to B_{12} supplementation. In any event, much wider study of vitamin B_{12} as a dietary supplement for children with growth failure was clearly called for.

Meanwhile, a number of other studies have been reported. Chow[4] noted favorable effects on weight gains, as did O'Neil and Lombardo;[5] although English workers, in an exceedingly brief statement,[6] deny such effects. Wilde,[7] utilizing the Grid technique to study growth failure in Aleutian children, found that 7 out of 9 subjects responded with an average increase of 0.45 *level/month* over prior rates of growth and this effect was attributed to B_{12} supplementation. On the other hand, comparisons between supplemented and unsupplemented premature infants have not yielded any differences in favor of the former.[8–10] Such null effects, however, should hardly have been unexpected, in view of the naturally high speeds (30–60 *lev./mo.*) which prematures regularly generate and maintain, as well as from the further fact that those who do so are certainly not in growth failure. Thus, while disparities in results are partly explained by differences in methods of dealing with child growth, they are due principally to unfamiliarity with the role which growth failure itself plays or can be made to play in studies of child nutrition.

* See Addendum.

The Nature and General Importance of Growth Failure in School Children

By its very nature, simple growth failure in children of school age is, without any reasonable doubt, a generalized deficiency state in which physical growth is measurably below par.[11-13] This disorder, arising as it does during the natural course of child life and under the very momentum of growth itself, is associated with slight but sufficient transgressions of nutritional law that help to produce it. As a result, it represents in human beings a condition that is virtually, if not entirely, comparable with various states of impaired growth that may be experimentally induced in animals, and like them, or better like an indefinite mixture of them, it may be expected to respond to a number of different specific or even nonspecific changes in nutritional or other habits. More directly, however, it is the existence of growth failure in certain children—not the fact that they are small, or slender, or young—that is decisive. Yet this distinction and what it implies have not received the attention they deserve, either from the standpoint of what growth failure signifies for the individual child, for the family, and the school, or, on the other hand, from the standpoint of the very important role it plays as a crucial test situation against which the worth of almost any school or child health project—not simply the value of B_{12} or of other supplements—may be gauged.

On the nutritional side, simple growth failure involves both substance as well as fuel debts[11] which must be paid up before recovery is fully achieved; but, in spite of those debts, it remains an entity that is remarkably free from specific organic lesions or symptoms. Its outward signs are few: loss of physique, fatigue, and dry skin are but rarely so pronounced as to be recognized on their own.[12] Indeed, even to the experienced eye, the existence of growth failure is less readily apparent in the subjects themselves than it is in their Grid record of physical growth and development,[2,3,11] a fact that is clearly illustrated by comparing the tell-tale evidence of Figure 1 with the photograph of Figure 2.

The example shown in Figure 1 is typical and it demonstrates two essential signs of simple growth failure quite unmistakably: (1) *loss of physique* along the entire segment (1–2) in the channel system, more especially as this girl drifted from the upper half of physique channel B_2 over into the lower part of B_3, and (2) *slow-down* in her rate of development from the time she entered school but particularly during the 2 years preceding B and thus during the period of greatest channel drift and greatest physique loss. Her average rate of progress for the 53 levels she actually advanced along AB during 63 months was 0.84 *lev./mo.*, whereas she would have originally been expected to average about 1.065 *lev./mo.* for the 67 levels along AD, her expected auxodrome. Slow-down along AB thus resulted not only in an accumulation of 14 levels of lag corresponding to the vertical difference between points B and D on her actual and expected auxodromes, respectively, but also in the accumulated fuel debt which is proportional to the cross-hatched area ABD and which amounted at B to 153,000 calories.[11]

Her response to 16 weeks of supplementation with vitamin B_{12} is likewise to be followed in both panels of Figure 1. The change in channel direction, with forward progress in B_3 in place of continued deviation into B_4, did not result in any appreciable *restoration* of physique, but it does indicate that further physique losses had been halted simultaneously with the upturn of her auxodrome along BC. The net effect of these changes, however slight they may appear in Figure 1, owing to scale, is to suggest the onset of a definite tendency toward recovery even though she continued to remain about 15 levels short of closing her lag-gap while proceeding along BC. This suggestion that she had entered upon a newly established recovery phase as a result of B_{12} supplementation is fully confirmed by an analysis of her rates of gain for the $2^1/_2$ years prior to B (i.e., during her years of lowest gain) and for the 9 months thereafter (the first 4 with, the last 5 without, B_{12}). These rates, accordingly, represent "before" and "after" values, respectively, and they correspond to the slopes of the two regressions that intersect at B in Figure 1.

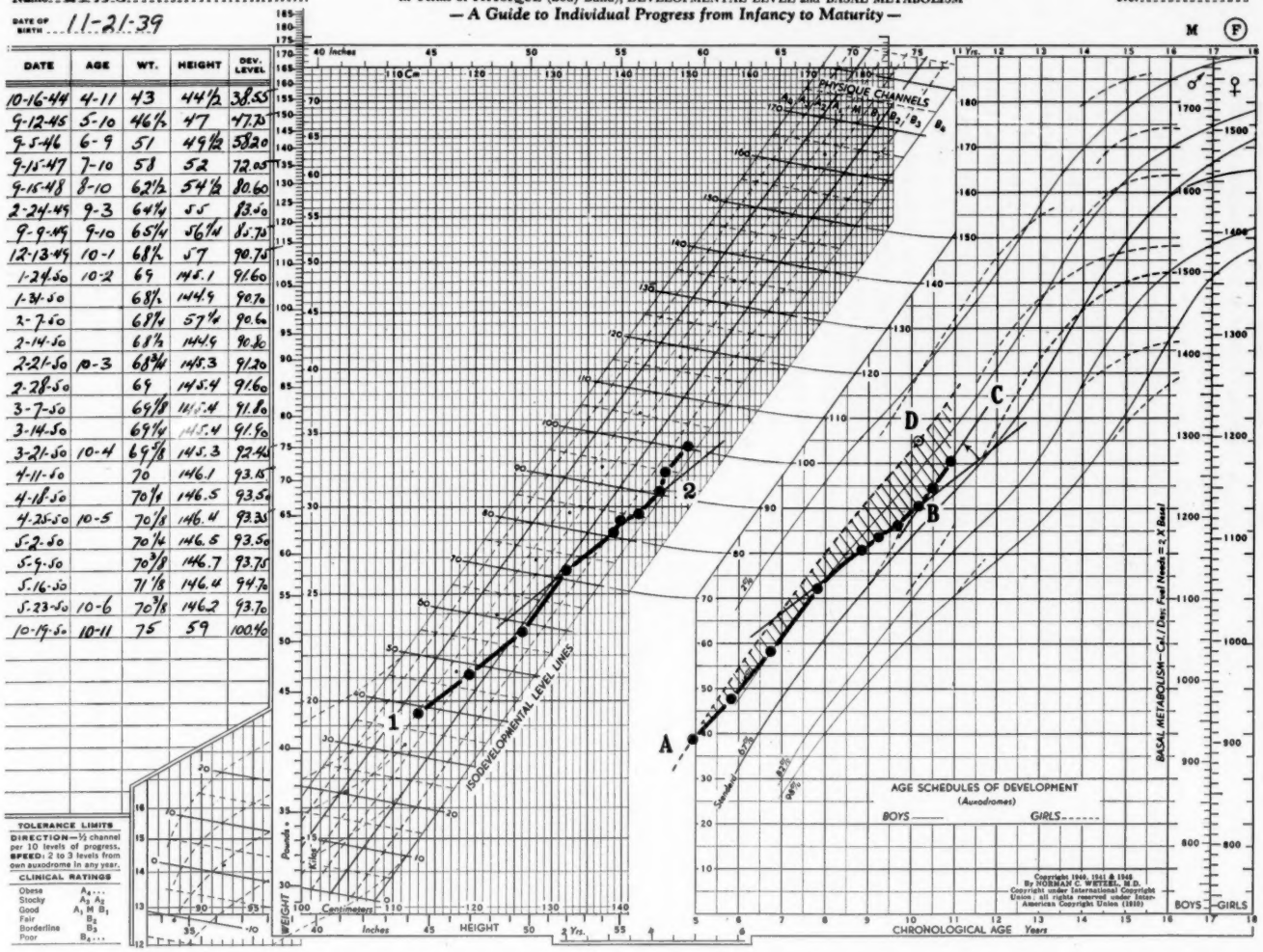
GRID for Evaluating PHYSICAL FITNESS
in Terms of PHYSIQUE (Body Build), DEVELOPMENTAL LEVEL and BASAL METABOLISM
— A Guide to Individual Progress from Infancy to Maturity —
Name C. M.
No. 50-12
DATE OF BIRTH 11-21-39
M (F)
DATE AGE WT. HEIGHT DEV. LEVEL
10-16-44 4-11 43 44½ 38.55
9-12-45 5-10 46½ 47 47.70
9-5-46 6-9 51 49½ 58.20
9-15-47 7-10 58 52 72.05
9-15-48 8-10 62½ 54½ 80.60
2-24-49 9-3 64¼ 55 83.50
9-9-49 9-10 65¼ 56¾ 85.75
12-13-49 10-1 68½ 57 90.75
1-24-50 10-2 69 145.1 91.60
1-31-50 68½ 144.9 90.70
2-7-50 68¼ 57¼ 90.60
2-14-50 68⅞ 144.9 90.80
2-21-50 10-3 68¾ 145.3 91.20
2-28-50 69 145.4 91.60
3-7-50 69⅜ 145.4 91.80
3-14-50 69¼ 145.4 91.90
3-21-50 10-4 69⅜ 145.3 92.45
4-11-50 70 146.1 93.15
4-18-50 70⅛ 146.5 93.50
4-25-50 10-5 70⅛ 146.4 93.35
5-2-50 70¼ 146.5 93.50
5-9-50 70⅜ 146.7 93.75
5-16-50 71⅛ 146.4 94.70
5-23-50 10-6 70⅜ 146.2 93.70
10-19-50 10-11 75 59 100.40
TOLERANCE LIMITS
DIRECTION—½ channel per 10 levels of progress.
SPEED: 2 to 3 levels from own auxodrome in any year.
CLINICAL RATINGS
Obese A5...
Stocky A3 A4
Good A1 M B1
Fair B2
Borderline B3
Poor B4...
PHYSIQUE CHANNELS
A5 A4 A3 A2 A1 M B1 B2 B3 B4
ISODEVELOPMENTAL LEVEL LINES
AGE SCHEDULES OF DEVELOPMENT
(Auxodromes)
BOYS —— GIRLS ------
Standard 87% 94%
A
B
C
D
1
2
HEIGHT
CHRONOLOGICAL AGE Years
BASAL METABOLISM—Cal./Sq. Meter/Hour Fuel Needs = % Basal
Copyright 1949, 1941 & 1948
By NORMAN C. WETZEL, M.D.
Copyright under International Copyright Union; all rights reserved under Inter-American Copyright Union (1910).

Fig. 1. A typical example of simple growth failure as revealed by plotting periodic heights and weights on a Grid. The essential signs of growth failure which this girl (shown in Fig. 2) revealed during her 5-year course of unsatisfactory growth between points 1 and 2 in the channel system, and along her actual auxodrome *AB*, are: (1) *loss of physique* from channel *M* to B_3 and (2) *slow-down* in the rate of development which would normally have carried her along the expected auxodrome *AD*. The vertical distance *BD* of 14 levels represents growth lag at *B* and is equivalent to about $1^1/_4$ years' development. The character of growth throughout her Elementary School years up to points 2, and *B* is typical of the growth failure group of children in the Nutrition Study prior to supplementation. See text for discussion of her response to vitamin B_{12}.

Numerically, they work out as follows:

Before:	0.666 ± 0.054	*lev./mo.* (4 *d.f.**)
After:	1.087 ± 0.056	" (15 d.f.)
Response = Difference:	+ 0.421 ± 0.092	*lev./mo.* (19 *d.f.*)

* *d.f.*—degrees of freedom.

so that $t = 4.55$ (before rounding) and p is very considerably less than 0.001 even for the 2-tail test. In applications of this type, however, the single-tail t test is employed since it is difficult to conceive of B_{12} inducing a child to gain less rapidly than it did during the prior control period. But if the "after" slope turns out to be less than the "before" rate, as sometimes happens, the "negative" response, though actually representing outcome so far as change in growth rates is concerned, would hardly be attributable to the supplement so much as it would be to many other factors that do cause a child's growth to slow down.

The curves of Figure 1 thus define the more important features of simple growth failure as this is traced out year after year in a child's Grid record, and they illustrate, in particular, the result so frequently encountered that growth failure, left to itself, tends to get worse. It is very striking, indeed, that the only time during this girl's entire school career of 6 years in which she even came close to "holding her own" or to showing any tendency to reverse the unsatisfactory trends that had persisted ever since she entered school, coincided exactly with the 4-month period of vitamin B_{12} supplements following the observations at points *2* and *B*. The evidence that this is hardly a chance coincidence is given, of course, by the 4.55 value of t reported above. Thus one may infer that, without supplementation, the girl would have lost still more physique by deviating over into channel B_4, and that she would have accumulated still more lag as well as an even greater fuel debt than she did —provided only that no other agencies had intervened and produced a set of effects similar to the B_{12} response. Finally, since the results in Figure 1 represent, at best, only partial recovery from moderately severe growth failure, they also illustrate the rather common finding that complete recovery is more successfully and more readily achieved under institutional care than it is in the environment which originally permitted growth failure to develop in the first place.

Fig. 2. A grip strength performance test by the girl whose Grid record is shown in Figure 1.

Significance of Growth Failure in the School Health Program

For the better part of the past decade a greater and greater share of the work carried on by the Medical and Health Departments of the Shaker Heights Schools has been devoted to those pupils who have developed the pathognomonic evidence of growth failure in their own Grid records which has just been described for the example in Figure 1.

A main reason for the ever-increasing interest and effort devoted to numerous aspects of this problem is that the prevalence of growth failure in the Shaker Heights Schools is essentially what it is elsewhere, despite the socio-economic fact that these schools are located in a high-income suburban community. This area is not one that is characterized by

to about 1¼ years' development. The character of growth throughout her Elementary School years up to points 2, and *B* is typical of the growth failure group of children in the Nutrition Study prior to supplementation. See text for discussion of her response to vitamin B_{12}.

marginal living. Its children and its general population are not obliged to subsist on marginal diets. It is not in the torrid zone; it is not depleted of protein, and there is certainly no Kwashiorkor reported in the neighborhood; yet simple growth failure exists in the usual ratio of about 1 in 3 despite some opinion, but no facts, to the contrary.

Viewed from the school playground, the need for dealing with simple growth failure is rarely apparent. Because of its subtle, insidious, and elusive nature (Fig. 1), this disorder passes unsuspected for the most part through classroom and clinic in the guise of children who are ostensibly well as long as they are able (Fig. 2) to attend school and participate in regular activities. Its mark, however, and its traces through preceding months and years are to be found instead, as Figure 1 shows, in a child's own record of growth and development once this has been plotted out from sequential data on weight and height.

When Elementary or Junior High records are periodically reviewed, examiners are invariably impressed with two contrasting facts: (*a*) the steady regularity with which 2 out of 3 boys and girls follow out their own Grid patterns of development, and (*b*) how stubbornly simple growth failure, once established, tends to persist and, indeed, as Figure 1 clearly shows, to get worse in the same children year after year.

What is thus being observed is an entity at work that lowers physique, lessens physical vigor, and slows down the progress of all growth and development. Efforts to handle this problem through periodic health reports or consultations have, in the main, achieved much less than had been intended, for later investigations with exasperating frequency have shown "little or no improvement." Over the years we have consistently employed close follow-up with repeated medical examinations, reports, parent-teacher and private physician consultations, all involving exchange of information intended to form the basis for recommendations suited to individual needs: home life and school progress, both academic and extra-curriculuar, have received attention; change in curriculum, restriction of athletic or gymnasium privileges, extra rest hours, relief from homework, television restraint, and similar measures have all been tried from time to time without producing the results that had originally been expected of them.

Meanwhile, we have had the unwanted opportunity of seeing the incidence of growth failure increase, and we have been obliged more often to watch it increase in individual boys and girls—as it did in Figure 1—than to see it vanish as a result of suggestions from any source.

Perhaps the most compelling reason for devoting more and more intensive study to the problem of growth failure resides in the plain fact—and we have had abundant evidence over the years to support it—that physical growth failure invariably hampers academic progress and achievement. That it also detracts from physical and athletic performance goes without saying. Since none of these conclusions is any longer in serious contention among us, as they once were, we have come to suspect that the consequences of growth failure flow over into every aspect of child life and that they can be discovered, if looked for, well beyond the schoolyard limits themselves. Whether as cause or as effect, we have learned that this distinctive entity exists at the core of every child problem no less than it exists in every problem child. On the other hand, the records of honor students and champion athletes offer a conspicuous and a challenging contrast: what imperfections of growth or growth trends they show are slight and, at the most, of evanescent duration. These things being so, there exists somewhere the responsibility not only for identifying growth failure as early as possible, but also for attempting to prevent its taking the "course of least resistance"—namely, what Figure 1 shows—that of getting worse. What many must learn, including pediatricians, is that growth failure is not openly apparent (Figs. 1 and 2) and that the needs of a child so handicapped are easily overlooked; they must learn, too, that efforts to deal successfully with growth failure will call for more cooperation and understanding on the part of parents, school personnel, and private physicians than is ever demanded for

occasions short of epidemics. The clear objective of all such efforts must be to restore physique and to repay fuel debts, but these ends cannot be achieved without direct action that provides a good diet and its effective utilization—with all that the latter implies—for, regardless of original cause, nutrition is always involved in the processes that lead to the resumption of growth and ultimately to recovery from growth failure.

As for contributing causes, the list reported almost 10 years ago is still valid:

> ". . . unsupervised diets, poor preparation and selection of foods, inadequate milk, poor home management, with domestic stress and strife even where socio-economic conditions were otherwise satisfactory, repeated infections, allergy, general hygienic neglect, dental caries, not doing well at school but quite regular attendance at 'movies.'"[13]

The impact of television is regarded by some as a possible new addition to this list. On the other hand, "adherence to family-type" cannot be accepted as a main cause of simple growth failure such as that illustrated by the example in Figure 1 without at the same time accepting Williams' concept of genetotrophic disease and his rationale of unusually high requirements for various nutrients.[15]

The Nutrition Study Groups

Simple growth failure has been studied by the Medical and Health Departments of the Shaker Heights Schools since 1941, but it became a subject of special interest when the Grid was adopted and established as the official school health record throughout the system a few years later. As a result, about 4500 long-term records have been continuously available for analysis and follow-up, among which are those of senior high students whose earliest data for 1940–41 considerably antedate the discovery of the very supplement (vitamin B_{12}) which some of these children were later to receive. The entire set of Grid records is subject to continuing review and classification into 3 groups: *satisfactory*, *unsatisfactory*, and *questionable* growth—from each of which the Nutrition Study draws its members by invitation.

Children with satisfactory growth compose about $^1/_5$ to $^1/_3$ of all those in the Study. These serve as "Normal Controls" and, as such, receive no supplements. The remainder are "Growth Failures" of the type illustrated in Figure 1, some with moderate, others with more severe, forms of this disorder. The average value of lag, for example, was 14 levels, with a range of 5–30 levels and the duration of failure extended from $1^1/_2$ to 7 years. These values are quite representative of the degree of failure commonly found among elementary school populations in the 4th, 5th and 6th grades.

Methods and Procedures

Weights and heights along with other measurements to evaluate physical performance (grip and back strength) were originally taken each week by a team of 4 persons assisted by the regular school nurses and occasionally by principals who acted as recording clerks. This experience showed that over-all efficiency could be increased by enlarging the number of children in the Nutrition Groups with a reduction from weekly to monthly measurements. Regular platform beam balances were employed with usual precautions as to calibration and check. For convenience and consistency, stature was measured either with a portable anthropometric rule and angle, or by means of a fixed wall scale, observing Krogman's directions[14] as closely as possible. Measurements were taken to the nearest $^1/_4$ pound and millimeter or $^1/_8$ in. respectively, the corresponding Grid level values being computed to 4 significant figures (i.e., second decimal; see data tabulated in chart of Fig. 1) with an error of less than 5 units in the last figure.[13]

A brief physical examination by a physician was given each child each week during the first year, with special reference to the condition of the hair, skin, conjunctivae, nose, throat, tongue, mucus membranes, and cervical lymph nodes—in order to detect the earliest signs of upper respiratory tract infection, but also to note changes that might occur during supplementation. Later, annual, semi-annual, or more frequent medical examinations were

given as required. All subjects, however, were under daily observation by the school nurses who referred children for medical check as necessary. In these examinations and inspections no specific lesions were encountered that could be associated with possible B_{12} deficiency.

To assure minimum loss of scholastic time, a strict schedule for examinations and measurements was maintained. During successive weeks, for instance, a given child would be put through the weighing, measuring, testing, and examining routines within 10–15 minutes of the same hour on the same week day, thus, providing almost exact 7-day intervals between successive observations. Similar arrangements applied when observations were made at monthly intervals. All children were measured between 10 A.M. and Noon in order to reduce fluctuations and particularly those associated with breakfast, recess, and lunch. All readings were taken by observers working in pairs without knowledge of previous values, though frank discrepancies as noted by assistants were called upon for immediate check.

Supplements of vitamin B_{12} (2×5 μg. crystalline* or concentrate equivalent†) in tablet form were administered orally, once a day, by the school nurses, complete ingestion being verified and recorded. Saturday and Sunday supplements were "doubled-in" on Fridays and Mondays. As a rule, the regular period for supplementation was confined to the second semester of the school year particularly to assure that growth had been acceptably stable during the 5 months immediately preceding supplementation. Home visits were made by the nurses to administer B_{12} in case of a child's absence. Except in a few instances, supplements were not provided during the 7 days of the Easter vacation. No supplements, of course, were given without explicit written permission from the parents who, as a matter of policy, are continually advised to consult their own physicians on all health problems discovered through routine check-ups.

Control supplements consisting of Lactose, U.S.P., 0.32 Gm./day, in tablets of various sizes, shapes, and colors have been employed from time to time either preliminary to eventual supplementation with B_{12} or in parallel growth failure groups in order to check possible indirect (e.g. psychological) effects, but no significant increases over prior rates of growth have been encountered with supplements of this kind. The more usual outcome, in fact, has again been that of continued slowdown, as represented, for example, in a typical "response" to Lactose, made by a group of 14 growth failures, namely, -0.036 ± 0.060 *lev./mo.*, the latter value being considerably removed from $+0.3$ which must ordinarily be exceeded in groups of that size to attain significance at the 5% level of confidence (*cf.* Table I). Lactose supplements, in other words, have not led to changes in growth rates comparable with those for Groups *B* and *C* of Tables I and II.

Results and Discussion

I. Groups A, B, C, and D— 60 Subjects— Crystalline vitamin B_{12} only—Simple Block Design—Tables I–IV

Over-all response to supplementation in this series is summarized in Table I, separate values for boys and girls being given in Table II. Before and after values, as well as differences, are shown along with their standard errors for the two groups of growth failure children who received B_{12}, namely, groups *B* and *C*, for the 20 normal controls comprising group *A*, and finally for the unsupplemented growth failure controls in group *D*.

A total of 23 out of 36 children in groups *B* and *C* who received B_{12} supplements for 16 and 6 weeks, respectively, responded definitely to them. This figure is slightly larger than the 5 of 11 originally reported for institutionalized children in the FAC Study, but it does not exceed the latter ratio significantly.

Mean responses as represented by before and after differences for the supplemented groups *B* and *C* show statistically significant growth effects. In the *B* group, $p < .001$, but $p < .05$ in group *C*, the latter having received B_{12} for only 6 weeks. The number of posi-

* Kindly supplied by the Medical Division of Merck & Co., Inc. of Rahway, N. J.

† Furnished through the kindness of Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

TABLE I

Summary of Responses in Groups *A*, *B*, *C*, and *D*; Incidence, Mean Effects and Standard Errors

Group	No.	No. Positive Responses	%	Rate of Gain—Level Lines per Month		
				Before	After	Difference
A. Normal Controls	20	—	—	1.102 ± 0.042	1.172 ± 0.068	0.070 ± 0.048
B. Growth failure—16 weeks' supplementation	20	16	80	0.693 ± 0.053	1.293 ± 0.093	0.600 ± 0.091*
C. Growth failure—6 weeks' supplementation	16	7	45	0.860 ± 0.10	1.26 ± 0.17	0.40 ± 0.17†
	36	23				
D. Growth failure—unsupplemented	4	0	0	0.62 ± 0.13	0.50 ± 0.54	−0.13 ± 0.60

*$p < 0.001$; †$p < .05$. Subjects in *B* and *C* selected by randomization; withdrawals from *C* carried along as *D*.

tive responses is also greater in group *B* but their prior rate of gain was slightly lower than the corresponding group *C* mean, although both groups gained alike while under supplementation. Mean values for boys and girls were practically the same (Table II) except in group *C* where the difference between the two sexes, though significant at the 5% level, is just barely so.

As explained in connection with the example of Figure 1, growth responses to supplementation always involve *two* before and after comparisons, namely, changes in channel as well as in auxodrome slopes, the former representing changes in physique, the latter changes in level rate of gain, each with respect to its own prior (control) value. Each thus leads to differences that will be $\begin{matrix}>\\=\\<\end{matrix}$ 0. For practical purposes, however, responses to supplementation, or to other conditions are sufficiently represented, especially during their earliest phases, in terms of rate changes alone. Hence, when the "after" > (exceeds) the "before" rate of gain, the "response" is said to be "positive" (cf. Fig. 3); the question as to whether or not an individual difference or response is statistically significant depends, of course, on the precision with which such differences can be estimated from the number and reliability of the data that are available for both before and after periods. Thus, while 16 subjects in group *B* of Table I showed an increase over prior rates, i.e. positive responses, as just defined, 4 showed either 0 or negative differences, which, nonetheless, were included in the group estimates, so that the latter represent actual *net* effects. Despite this, however, the group *B* and *C* responses are clearly significant.

TABLE II

Comparison of Boys' and Girls' Responses in Groups *A*, *B*, and *C* of Table I

Group	No.	No. Positive Responses	%	Rate of Gain—Level Lines per Month		
				Before	After	Difference
A. Normal Controls						
Boys	9	—	—	1.056 ± 0.068	1.138 ± 0.084	0.082 ± 0.049
Girls	11	—	—	1.140 ± 0.052	1.20 ± 0.11	0.059 ± 0.079
B. Growth failure—16 weeks' supplementation						
Boys	8	6	75	0.78 ± 0.12	1.32 ± 0.13	0.54 ± 0.11
Girls	12	10	83	0.634 ± 0.037	1.28 ± 0.13	0.64 ± 0.13
C. Growth failure—6 weeks' supplementation						
Boys	6	1	15	0.756 ± 0.087	0.739 ± 0.078	−0.017 ± 0.14
Girls	10	6	60	0.93 ± 0.16	1.57 ± 0.22	0.64 ± 0.23

All values in Tables I and II are *net*, that is, they include the response of every child in a given group regardless of whether or not that was significant, or again, whether the after rate turned out to be greater or less than the control rate. On the average, the children who were supplemented for 16 weeks (Group *B*) showed a 0.60 *lev./mo.* increase over and above their 0.693 rate prior to supplementation, the standard error being 0.091 so that there can be no question as to statistical significance. Groups *A* and *D* in Table I showed "no-difference" for the corresponding "before and after" period of observation. This, of course, is as it should be. Moreover, real consistency in growth trends is reflected by the small standard errors for the normal children in group *A*. The group *D* "after" rate actually turned out to be less than their prior rate by —0.13 *lev./mo.* and thus illustrates the fact, repeatedly emphasized, that growth failure, left to itself, tends to get worse, though the drop is not, in this case, significantly different from 0. All values in the "after" column, with the exception of *D* are essentially alike, a result that warns of what is apt to happen when attempts are made to evaluate vitamin effects by the method of parallel group comparison so commonly employed in animal nutrition rather than by the *before* and *after* technique.

When the data of Table I are reduced to the analysis of variance form, as given in Table III, the conclusions already reached are again very strongly supported. In particular, *F* for groups *A*—*D*, with 3 and 56 *d.f.* is significant at the 1% level which is to say that the mean values of *A*, *B*,..., are actually different from each other. Examination of the 3 separate mean squares corresponding to the orthogonal comparisons in Table III shows that only the last is significant, with *p* almost exactly equal to 0.001. Therefore, groups *A* and *D* may be considered to have behaved alike in that *neither* showed an increase over control rates; groups *B* and *C* behaved alike in that *both did* show such an increase, and, finally, all supplemented children (*B* and *C*) responded quite differently than all the unsupplemented subjects (*A* and *D*) did.

Since the *B* vs. *C* mean square is insignificant (boys and girls taken together) average response tended to be the same for those who received the supplements for 6 weeks (*C*) as for those who had B_{12} throughout the entire second semester (*B*). Continued supplementation, accordingly, did not further augment a response rate that had been generated during the first 6 weeks.

TABLE III

Analysis of Variance of Individual Responses to Vitamin B_{12} Supplementation for Groups *A*, *B*, *C* and *D*

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square
Groups: *A*, *B*, *C*, *D*..	3	3.6960	1.2320*
Normal vs. unsupplemented growth failures, i.e., *A* vs. *D*	1	0.1262	0.1262
16 vs. 6 weeks' supplementation, i.e., *B* vs. *C*	1	0.3762	0.3762
All supplemented vs. unsupplemented, i.e., (*B* + *C*) vs. (*A* + *D*)	1	3.1936	3.1936†
Residual (Error)....	56	15.1980	0.2714
Total	59	18.8940	

*$p < .01$; †$p \doteq 0.001$

For group differences, $F = 4.54$; $F_{.01} = 4.16$

For all supplemented vs. all unsupplemented, $F = 11.77$, $F_{.01} = 7.12$. This same comparison with 58 *d.f.* for error yields: $F = 11.80$; hence $t = 3.435$, so that $p = 0.001$ almost exactly.

This result, as it happens, is actually exemplified in Figure 3 (discussed below) wherein the first response *CD*, during 6 weeks of supplementation consisted of a greater elevation (1,2) above the control trend *AF* than the second response during $4^1/_2$ months' supplementation showed along (3,4) with respect to the same control regression, *AF*, which traverses the $p = 0.001$ confidence band. Thus, although response I exceeded II, since its *change* in rate was greater, the total level gain, associated with the upturn in I, was considerably less than in II because the rate along (1,2) endured for a much shorter period than the more prolonged elevation (3,4) did during the second period of supplementation. Consequently, whereas the "response to" or the "effect of" B_{12} supplementation is preferably measured and expressed in terms of change in rate itself, the ultimate benefit from such increased rates depends also on the duration through which they are maintained. Hence, a decision on how long such supplements might be continued depends, among other things, upon the amount of lag still remaining to be made up at any given time (cf. Fig. 1).

The highly significant result represented in Table III by the single degree of freedom for the comparison between all supplemented (*B* and *C*) and all unsupplemented children (*A* and *D*) with its m.s. of 3.1936 and $F = 11.80$, i.e., $t = 3.44$ and $p \doteq 0.001$, taken in conjunction with insignificant values for the two other *d.f.* indicates that crystalline vitamin B_{12} supplements were undeniably associated with the re-

sponses which groups *B* and *C*, and these alone, made; and, unless a chance event, with probability $p = 0.001$ had intervened, that the supplements were responsible for increasing the prior rates of groups *B* and *C* to the extent represented by the "before" and "after" differences in Tables I and II.

TABLE IV
Effect of Prior Rate on Response to Vitamin B_{12} Supplementation

Groups	Prior or Control Period Ranges—Levels per Month			Totals
	0 to 0.75	0.75 to 1.05	1.05 to 2.0+	
No. of positive responses....	20	2	1	23
No. of 0 (zero) and negative responses....	2	8	3	13
Totals.....	22	10	4	36

In Table IV, the proportion of positive responses to B_{12} supplements falls off considerably as prior control rates approach and exceed the normal value for school children of 1 *lev./mo.** This result has been confirmed in the factorial design of Series II (below) and it would appear to indicate that renewal of growth takes place preferentially in those with greatest need, that is, in those children who have been gaining most slowly during the period preceding supplementation. That it does not, however, exclude the possibility of a B_{12} effect when prior rates in growth failure are as high as 1 *lev./mo.* is shown by the two distinct responses made by the girl whose long record is illustrated in Figure 3.

* Attention should again be drawn to the important fact that 1 *lev./mo.* is a universally valid standard for the rate of gain in normal healthy children of school age and, as such, that it is *independent* not only of race, sex, socio-economic status, and relative growth advancement, but also of body measurements, e.g. of weight and height, as well as of physique and body size, and, finally—up to maturation—of age as well. This means that growth rates expressed in Grid *levels/month* are independent of level itself, and that levels as well as level rates are additive—a most important property not shared by weight or height, and a prerequisite that must be satisfied if analysis of variance is to be employed. For practical purposes, level rate of gain is thus subject to environmental factors alone, more particularly those concerned with food supply and its utilization for growth. Lastly, a warning on interpretation may be mentioned: the fact that a given child is, or has recently been, gaining 1 *lev./mo.* is a necessary but not a sufficient condition for inferring that "growth is normal." Other evidence, more specifically, absence of lag, and "up-channel progress" i.e. at constant physique, is required before growth failure can be ruled out.

II. Groups E and F—236 Subjects—Crystalline and Concentrate Vitamin B_{12}, 3×2^4 Factorial Design

In a similar but much more highly expanded 5-factor investigation involving 236 children, no differences were found for equivalent dosages of crystalline and concentrate forms of vitamin B_{12}, the mean being 0.244 ± 0.067 *lev./mo.* increase over prior rates. This value is again *net*, that is, it includes all responses, positive, zero as well as negative. While these results cannot be discussed in full here, it may be remarked that when corrections for differences in prior rate, sex, and other factors are made, mean effects are considerably higher (0.9 *lev./mo.* in certain groups) thus equaling and even exceeding values in Table I.

III. Two Different Periods of Supplementation in the Same Child—Case S.P.-44

This girl was originally one of the members of group *C* in Table I. Her first response to 6 weeks' B_{12} supplementation is shown by the segment *CD* in Figure 3, with prior control period *AC*. From *D* to *F* she received no B_{12}. Since the trend from *E* to *F* turned out to be no different statistically from the first control trend *AC*, a common regression *AF*, with slope 1.112 ± 0.023 *lev./mo.*, may be used for both comparisons. The "after" slope (1,2) during supplementation I was: 2.610 ± 0.41. Her second period of supplementation (II) resulted in the response *FG* with slope 2.159 ± 0.098 *lev./mo.* along the regression (3,4). It is obvious from these numerical values as well as from Figure 3 that both responses were highly significant.

IV. Caloric Intake

Unfortunately it was impossible to make a complete diet survey of all children participating in the Nutrition Study. Records on 45 boys and girls receiving either crystalline or concentrate vitamin B_{12} supplements have been very carefully analyzed from the stand-

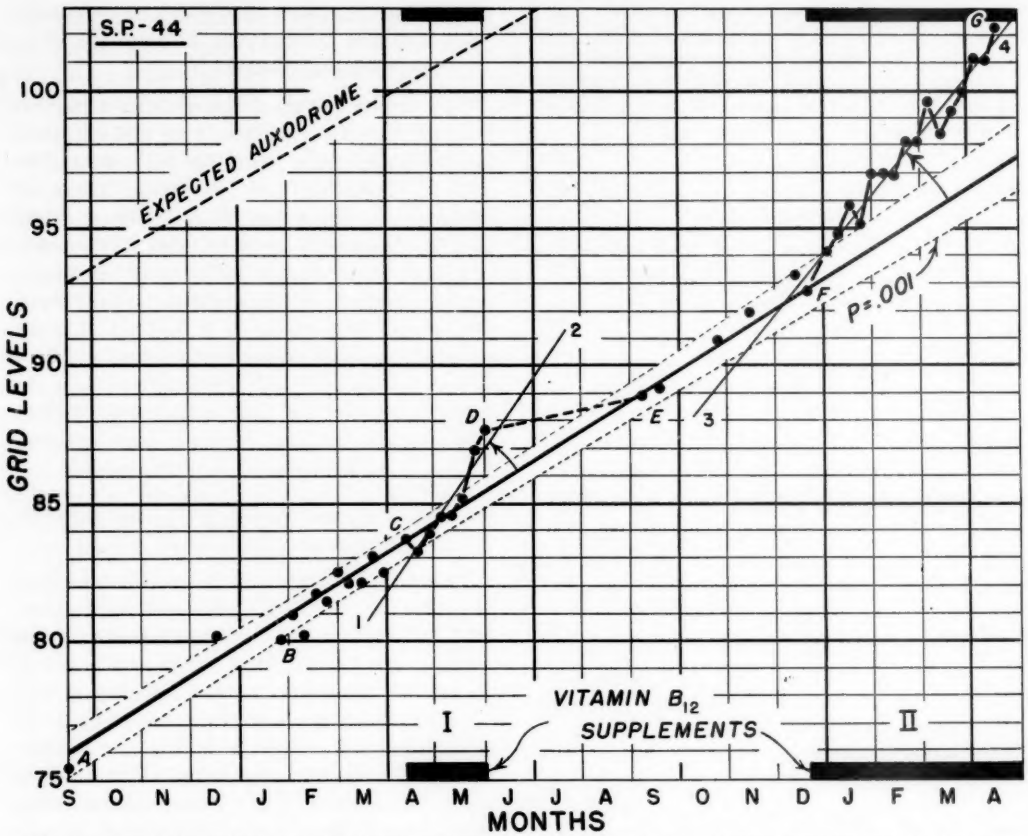

Fig. 3. Two independent and significant responses to oral vitamin B_{12} dietary supplements in the same child, S.P.-44. The first is shown by *CD* during a 6 weeks' period of supplementation (I), the second by the response *FG* during 4 months (II) of oral B_{12}. Note importance of scale magnification as compared with Fig. 1. The common regression *AF* with its corresponding 0.001 confidence bands represents both prior control periods *AC* and *EF*. This long-term auxodromic record shows maintenance of excellent statistical control, i.e., high stability during periods without B_{12}, so that deviations from the basic trend *AF* are associated with, and only with, each of the two periods of supplementation.

point of caloric intake, food choice, and diet composition, with a distinct advantage in all of these respects in favor of those children who showed positive and definite responses to B_{12}. The latter, in fact, had a mean caloric intake, based on level, of 246 ± 89 cal./day greater than those who showed no B_{12} response. This result, with $t = 2.76$, is again significant at the 1% level and it is completely in harmony with the view that fuel debts cannot be made up without overages beyond daily level needs.

V. Other Observations

No definite correlations have thus far been encountered between the growth responses and other measurements such as physical performance measured by change in grip, back or leg strength; nor with seasonal climatological changes in temperature, humidity, and barometric pressure, nor again with economic trends as reflected in various indexes.

Comment

Unless some extraordinary chance event, with a probability of less than 1 in 1000 trials had befallen this Shaker School Nutrition Study, it is impossible to avoid the conclusion that the vitamin B_{12} supplements and the

growth responses we have observed are related as cause and effect. From the clinical side, it is quite impossible, of course, to accept the idea that there exists but one cause of simple growth failure in school children. But, just as there would appear to be no such single cause, it is equally plain that no single remedy exists which could assure recovery from this disorder, or, even if one substance should seem to do so, that it would be acting alone. Hence, the role of vitamin B_{12} dietary supplements in inducing renewal of growth in children with simple growth failure would appear to be more that of a marshaling agent which effects reorganization of a variety of metabolic derangements involved in that disorder than that of meeting a single specific deficiency as it is considered to do in pernicious anemia. Consistent with this view are the recent studies of James and Abbott[16] who were able to show stimulation of protein synthesis associated with increased nitrogen and phosphorus utilization, with changes in uric acid excretion and with changes in plasma potassium values.

We were prepared, accordingly, for the possibility that still fewer of these children would respond to B_{12} supplements, living as they did under the "open" conditions of customary school attendance, variable home and outside influences, or pressures, as compared with the "closed" circumstances of an institutional program such as that carried out at the Children's Fresh Air Camp.

From one point of view the response rates appear to be comparatively high, yet, from another, they might be considered to be relatively low. It must not be forgotten that all values are *net*, so that an average increase of 0.4–0.6 *lev./mo.* over prior rates, in even a single instance, would have its own proper worth. It would mean, concretely, an advantage of 6 months' extra growth and development within a single year, and thus a six months' step toward recovery and toward a physical state more nearly "up to par." This average must also be understood to imply that some children had accelerated considerably more than that; in fact, a few increased their prior rates by as much as 1.50–1.70 *lev./mo.* Certain individual subjects in this study, therefore, even without benefit of institutional management, were able, under regular home and school conditions, to generate after rates that amounted to 60–70% of those measured under the more highly stable conditions of the FAC group. This, of course, is consistent with other knowledge on the nature of growth failure and how it tends to respond to proper management, for it has long been realized that recovery is much more difficult to achieve at home than it is at an institution such as the Fresh Air Camp.

Conclusion

All of the foregoing evidence, therefore, supports the conclusion that vitamin B_{12} does exert a "growth-promoting-effect" *when given as a dietary supplement to children in growth failure*—and this evidence is exceptionally strong. There is less need of reaffirming such results than there is of extending observations in order that many agencies which help to determine, or are capable of influencing, these growth responses can be more clearly understood.

Finally, from the standpoint of the Nutrition Program as a whole, it should be remarked that the general benefits derived from the present study of vitamin B_{12} dietary supplements were felt well beyond the point at which individual children developed recovery responses. The most immediate reactions were noted, as might be expected, by the personnel of the medical and nursing departments, but almost simultaneously by teachers in the classrooms who became aware that at least some of the pupils were improving in behavior, attitude, and scholastic work—or that they were showing less strain and fatigue, or, on the other hand, greater interest and attention, and hence better all-around progress than before. Voluntary expressions of similar import were offered by parents. The fact that the children themselves were well disposed toward the program is attested to, of course, by the fine attendance record they made, and by their willingness to participate faithfully in the extra routine of all tests, measurements, and supplements.

Acknowledgments

We wish to express sincere appreciation for professional assistance, well beyond the call of duty, which has been contributed to the work of the Nutrition Study by the School Nurses and Secretaries, in particular by Miss Besse Phare, Miss Dorothy Swancott, Miss Barbara Hlavin, Mrs. Margaret Hurley, Mrs. Manuel E. Kuechle, Mrs. Elizabeth Beemer, and Mrs. Katherine Sia, as well as to the teachers and principals of the various schools in the Shaker Heights District. We are likewise deeply grateful to Dr. Francis Bayless and Miss Edna Chapman for blood laboratory work, and to Miss Esther Uhlman for diet surveys; to Barney Tautkins, Ralph F. Deucker, H. H. Young, Gene Myslenski, William Goellner, and David Hill for expert technical assistance in measurements and computing. It has been a pleasure to discuss statistical design, methods, and results with Prof. Fred Leone of Case Institute of Technology and with Dr. David Frazier. Yet, without the long interest, foresight, and tactful guidance of William Slade, Jr., Superintendent of Schools, neither the prior surveys on which the Nutrition Program so much depended, nor the Study itself, could have been carried out at this time. To his splendid leadership, we owe a particular note of appreciation.

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Addendum in Press

The investigation which English workers announced[6] as not confirming the FAC results[1] turns out, from later details (*Med. Offic.*: Apr. 5, 1952, 137) to have had little in common (methods, case selection, etc.) with the FAC study aside from B_{12} given orally to 418 children attending open-air schools but living at home—a sample more comparable with our Series II than with the FAC group. Differences in wt. and/or ht. gains were declared insignificant though no estimates of precision were given. From their data, however, overall response to B_{12}, expressed in Grid units, works out as: $+0.05 \pm 0.12$ *lev./mo.* (21 d.f.), the 5% confidence limit, +0.30, considerably overlapping our Series II mean: 0.244 ± 0.067 *lev./mo.* which, in contrast, carries more than a 1,000:1 chance of differing from 0. Consequently, their "null-effect"—though not different from 0, is, at the same time, *not significantly different from, and hence, actually compatible with*, our findings. Their standard error (0.12), notably large despite 3 to 4-fold greater replication, reflects inefficient design and method. Such inflation of error, inevitable in wt.-ht.-age averages,[13] cannot be overcome by mere replication, especially with subjects gaining more than 1 *lev./mo.* (see Table IV),

as the majority of their groups did. Even the unquestionable responses revealed by the Grid technic in Figures 1 and 3 could not withstand "dilution" by the data of 1 or 2 randomly selected children, not to mention their complete obliteration by being averaged with data from 400 or more!

Resumen

Crecimiento defectuoso en niños de escuela—Estudios ulteriores sobre los suplementos dietéticos vitamínicos B_{12}

A no ser que algún acontecimiento fortúito extraordinario sobreviniese en este estudio nutritivo en las escuelas Shaker—y la probabilidad de tal acontecimiento es menor de 1 en 1,000 pruebas—es imposible evitar la conclusión de que los suplementos vitamínicos B_{12} y las respuestas de crecimiento por nosotros observadas guardan una relación de causa a efecto. Desde el ángulo clínico, claro está, es imposible admitir la idea de que no existe sino una causa única del crecimiento deficiente en niños de escuela. Pero lo mismo que parece no haber tal causa única, es igualmente claro que no existe un remedio único que pudiera asegurar la recuperación en este desequilibrio, e incluso si tal substancia pareciera actuar de esa manera, que actuase por sí sola.

Estábamos, pues, preparados para la posibilidad de que todavía un menor número de estos niños respondiera a los suplementos de B_{12}, viviendo como vivían bajo las condiciones escolares corrientes y las influencias domésticas y exteriores variables, en comparación con las limitaciones de un programa institucional tal como el realizado en el Children's Fresh Air Camp.

Desde cierto punto de vista, los grados de respuestas parecen relativamente altos, pero desde otro ángulo, pueden ser considerados relativamente bajos. No debe olvidarse que todos los valores son netos, así que un aumento medio de 0.4—0.6 niveles por mes sobre los valores anteriores, incluso en un caso único, tendría su propio valor. Significaría, concretamente, una ventaja de 6 meses de crecimiento y desarrollo adicionales durante un solo año, y así de un paso de 6 meses hacia la recuperación y hacia un estado físico más cerca de lo normal. Este es un promedio, y hay que no olvidar que algunos niños habían accelerado mucho más; en efecto, algunos adelantaron su velocidad anterior hasta 1.5—1.70 niveles por mes. Ciertos casos aislados, aun sin beneficio de la dirección institucional, fueron capaces, bajo las condiciones normales del hogar y de la escuela, de iniciar velocidades posteriores que igualaban a un 60–70 por 100 de las medidas bajo las condiciones más estables del grupo FAC. Lo que, claro está, es conforme a otros conocimientos de la naturaleza del crecimiento defectuoso y de como tiende este a responder a un control adecuado, pues se conoce hace tiempo que es mucho más difícil lograr la recuperación en casa que en un instituto tal como el FAC.

Todo lo expuesto sostiene la conclusión de que la vitamina B_{12} ejerce un efecto "estimulador de crecimiento" *cuando se da como suplemento dietético a niños con crecimiento deficiente*—y esta evidencia es extremadamente sólida. Hay menos necesidad de reafirmar tales resultados que no de extender las observaciones, para que los muchos factores que ayudan a determinar, o que son capaces de influir sobre estas respuestas de crecimiento puedan llegar a ser más claramente conocidas.

Finalmente, hay que notar que los beneficios generales derivados del estudio corriente de los suplementos vitamínicos B_{12} se han hecho sentir más allá del punto en que casos aislados alcanzaron respuestas recuperativas. Las reacciones más inmediatas eran apreciadas, como era de esperar, por el personal de los servicios de medicina y enfermería, pero casi simultáneamente por los maestros en las clases, quienes notaban que algunos de los estudiantes mostraban menos tensión y fatiga, o, expresándolo de otro modo, mayor interés y atención, y por eso un mejor progreso general. Expresiones voluntarias de sentido semejante eran ofrecidas por los padres. El hecho de que los mismos niños estaban bien dispuestos para con el programa seguido se atestigua por su excelente asistencia, y por su participación fiel y de tan buena gana en la rutina suplementaria constituida por todas las pruebas, mediciones, y suplementos.

ALCOHOLISM *as a* NUTRITIONAL PROBLEM

By ROGER J. WILLIAMS, PH.D.

IT HAS LONG been recognized that alcoholism may give rise to serious nutritional problems in its victims, but only recently have our observations revealed that nutritional deficiencies play an important role in the etiology of alcoholism itself.

It may be well to point out, since there is some room for misunderstanding, that I and my colleagues designate as "alcoholism" that type of alcohol consumption which *leads progressively to more drinking and to a partial or complete incapacity on the part of the individual to do useful work in society.* On the basis of this concept, alcoholism may be of varying severity; in mild cases the individual's capacity is interfered with only slightly—hence the difficulty in arriving at satisfactory statistics. Certainly, however, an individual whose drinking is *stabilized* (even if at a high level) and who is able to perform satisfactorily as a member of society, is not afflicted with what our group regards as typical alcoholism.

The conclusion that nutritional deficiency is a basic cause of this type of uncontrolled liquor consumption is based upon three lines of evidence: (1) that growing out of recent findings in the field of biochemical genetics; (2) that from direct animal experimentation; and (3) that from clinical findings.

From the Biochemical Institute and the Department of Chemistry, The University of Texas, and the Clayton Foundation for Research, Austin, Texas.

Based upon biochemical-genetic relationships brought to light largely through the investigations of Beadle and coworkers[1] is the inescapable fact that each individual human being must possess by inheritance a distinctive set of metabolic machinery in which the numerous enzyme systems vary somewhat in efficiency. This means that of the numerous transformations which are essential to life, some, in a given individual, are accomplished with comparatively greater and others with comparatively lesser facility. This in turn leads inevitably to the conclusion that the nutritional needs of individual people cannot all be the same from the quantitative standpoint. The building of specific enzymes, the flavoprotein enzymes, for example, does not take place with equal facility in all individuals and since riboflavin is a constituent of these enzymes it seems certain (and in accordance with laboratory findings) that different individuals require somewhat different amounts of dietary riboflavin.

The discovery by Mitchell and Houlahan[2,3] of "partial genetic blocks" adds another link to the chain of evidence in favor of individuation of nutritional needs. Genes which control a particular chemical transformation are not usually destroyed by mutating agents; they may be slightly or seriously impaired. A particular transformation therefore may take place slowly and require a larger concentration of substrate in order to keep pace.

Individual Patterns

Not only do these basic findings make individuation in nutrition inescapable, but extensive studies carried on in the author's laboratory[4] have demonstrated that the end products of metabolism, as determined, for example, by paper chromatographic analysis of urine, reveal the existence of distinctive individual patterns. These findings apply to experimental animals on identical diets, where the differences in patterns are clearly of genetic origin, and to human beings on self-selected diets, where the evidence also indicates that crucial differences are of genetic origin. These findings are in a sense an extension of the work of Garrod[5] on "inborn errors of metabolism" which are known to be inherited, except that our findings apply to all individuals, each of which exhibits his own individual pattern. These findings are completely in line with the concept of individuation with respect to the quantitative nutritional needs, and with the existence of patterns of nutritional requirements which are distinctive for each individual.

The animal experiments bearing upon the relationship between deficiencies and alcoholism have been described elsewhere,[6,7,8] but their essence can be given in a short space.

Individual rats on a stock diet exhibited markedly individualistic responses when they were offered a choice between water and 10 per cent alcohol. Some drank alcohol heavily from the start; some drank none over a period of months in spite of the fact that the positions of the bottles were interchanged daily, forcing them to make a deliberate choice. Others drank moderately, others spasmodically, still others drank progressively more as the experiment proceeded. If the performance of a group of rats had been averaged together as is customarily done, the entire significance of the experiment would have been lost.

Changing diets had a revolutionary effect on the drinking patterns of the rats. When a group was placed upon a marginal diet—marginal particularly with respect to the B vitamins—all of the rats drank heavily within a short period of time. On the other hand, when the rats were placed upon diets abundantly furnished with all the nutrients required by rats, none of them consumed alcohol beyond a low level. Furthermore when animals were drinking heavily on a marginal diet and were supplied with an abundance of the missing nutrients, their alcohol consumption often dropped to zero overnight and was maintained at this level as long as the nutrients were supplied.

Interpretation

The obvious interpretation of these findings is as follows: Each individual animal has nutritional needs that are quantitatively distinctive. On the stock diet some rats were getting an abundance of everything, and because no deficiency existed for them, they had no marked tendency to drink alcohol. On the marginal diet all animals developed deficiencies and they all had a substantial appetite for alcohol. On the abundant diet, which contained generous amounts (several times the minimal needs) of many of the nutritional elements, none of the rats developed deficiencies and none drank appreciable amounts of alcohol.

Why various deficiencies should cause an appetite for alcohol is not understood; however, that deficiencies *do* induce alcohol consumption we regard as a fully established fact, as far as rats are concerned, since we have observed it hundreds of times. That the animals on a diet which does not furnish sufficient raw materials for the synthesis of various metabolic enzymes are seeking a source of easily derived calories seems a plausible explanation, but, regardless of the explanation, the fact remains that *dietary deficiency leads to greatly increased alcohol consumption.*

Deficiencies Differ

One of the complicating factors which arises in connection with this study is that the deficiences which arise in individual animals are not all the same. It is clear from our studies that in different animals, different deficiencies exist, but that they lead to the same increased alcohol consumption.

In the original colony of rats which we

investigated, we found it possible to control the amount of their drinking almost perfectly by the use of known dietary factors. Rats from this original colony breed true, and have maintained similar drinking patterns as influenced by nutritional supplements over a period of years. Rats of other strains—and a number have been investigated[9,10]—often develop deficiencies for unknown nutrients, and their alcohol consumption in some cases can only be alleviated by supplying nutrients of an unknown nature. This is in line with the finding of Murdones, *et al.*[11,12]

Effect of Vitamins

Our experience in this particular may be made clear by reporting composite results involving a large number of rats representative of all the strains which we have studied. On a marginal diet such as we used,[7] substantially all of the animals will drink at a high level. If ample supplies of the better known B vitamins (excluding B_{12}) are added to the diet, a significant number (but a small minority of the whole group) are "cured" and never drink substantial amounts of alcohol as long as the improved diet is maintained. If *in addition* vitamin B_{12} is supplied, the number of "cures" is greatly increased, so that now perhaps one half of the animals respond. By adding supplementary vitamins A, D, E, and a source of unsaturated fatty acids, the proportion of cures is substantially increased, but some of the animals still have an appetite for alcohol. When antibiotics (terramycin for example) and preparations of unidentified nature from yeast are added, a large percentage of the animals have their appetites for alcohol abolished or at least greatly diminished (unpublished data). Some of these unknowns are being investigated in our laboratories.

The exact results obtained will depend upon the make-up of the original rat population used, but in any case it is perfectly clear that on a marginal diet all animals will drink substantial amounts of alcohol, but that there will be progressively fewer and fewer animals which have an appetite for alcohol as the diet becomes abundantly supplied with additional nutritional factors.

Clinical Applications

In view of the clear-out relationship between nutrition and alcohol consumption in rats, the question as to the applicability of these findings to human beings becomes paramount. Certainly in human beings all sorts of psychological and sociological forces come into play, and the problem of alcoholism as it exists in human beings is far different from that involved in the consumption of alcohol by rats in individual cages. Before dismissing the parallel too lightly, however, it should be recognized that a vast proportion of what we know about human nutrition was learned by studying the nutrition of experimental rats.

A long-term, large-scale, controlled experiment is under way at the Harvard School of Public Health under the direction of Dr. Fredrick Stare, to determine the efficacy of a specific supplement of known vitamins in the treatment of alcoholics. This study will not be completed for about two years, but a preliminary report[13] indicates that the findings are in accord with the animal findings, and that nutritional supplements cause a decrease in alcohol consumption in human patients. Many patients experienced a diminished craving for alcohol as a direct result of vitamin administration, and most of them reported an improved sense of well being.

It is hoped that the above mentioned study, *in which the element of suggestion is eliminated by the use of placebos,* will establish in a definitive manner whether or not nutritional supplements will, *in some cases,* abolish alcoholic craving. If the principle is established, it will be in order to modify and improve the supplements, introducing new vitamins, etc., as they become available, to the end that all alcoholics may be helped.

Smith, *et al,* [14] have also reported on a few cases in which alcoholic patients have been greatly benefited by the same nutritional supplements.

Before the above mentioned clinical experiments had been reported, my associates and I became fully convinced, on the basis of personal observations, that for some individuals nutritional supplements may bring about dramatic results. It is fortunate, as far as

generating enthusiasm for the possibilities of the treatment is concerned, that the first patient (who had been a heavy drinker for 20 years and an alcoholic for 10, and had not reacted favorably to psychiatry or the Alcoholics Anonymous program) should have been transformed, over three years ago now, into a moderate drinker who has no difficulty as long as he takes the nutritional supplements. As described elsewhere,[15] some individuals have had their difficulties completely removed within about two weeks; for others it has taken longer to produce benefits; and for still others the beneficial effects have been fleeting or questionable. Personal talks with several individuals who now can drink or not as they choose, and who previously could not, together with the background information and observations with animals, have convinced me of the validity of the principle.

Need for Investigations

It is important, however, that the nutritional treatment we have devised (or improved versions of it) should be tried out as widely as possible, so that the potential benefits will be available to the vast numbers of people who have more or less difficulty in controlling their drinking, and to the oncoming generation who may be prevented from falling into the morass of alcoholism by judicious nutritional supplements. One study[16] has indicated strongly that there are recognizable characteristics present in the metabolic patterns of potential alcoholics, which should make it possible to identify and forewarn vulnerable individuals.

The fact that the treatment or prevention of alcoholism by nutritional supplements has been emphasized does not deny the importance of psychological and sociological forces. It is well known that psychological stresses alter body chemistry, and it could be that these stresses help to create or at least to accentuate body deficiencies by impairing absorption or assimilation or by direct effect on particular enzyme systems. There is no hope of understanding completely all the factors involved in alcoholism until we understand human beings in their entirety, but the nutritional factors appear at present to constitute an important key.

Genetic Factors

The nutritional approach to alcoholism may have very widespread implications because of its bearing on the concept of genetotrophic diseases.[17,18] These diseases, of which alcoholism appears to be an example, are those which arise because the genetic pattern of the individual calls for an augmented supply of a particular nutrient or nutrients, which is not supplied by the food consumed. Such a disease can presumably be completely obviated by suitable nutritional supplementation. As has been indicated elsewhere, there may exist a multitude of such diseases.

If the nutritional treatment of alcoholism is valid, there is hope that a vast number of other obscure diseases may yield to nutritional treatment when the genetotrophic principle is applied intelligently, using all of the modern and currently discovered factors in nutrition.

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Resumen

El alcoholismo como problema nutritivo

Una deficiencia nutritiva es sugerida como la base para el alcoholismo. El autor expone su tesis con tres lineas de evidencia: (1) descubrimientos recientes en el campo de la genética bioquímica, que muestran la individuación del mecanismo metabólica, y de ahí de los requerimientos nutritivos; (2) experimentación directa en animales; (3) datos clínicos.

Experiencias en una colonia de ratas mostraron: (1) que la respuesta al alcohol de los animales alimentados con una dieta básica varió marcadamente según el individuo; (2) que los alimentados con una dieta marginal (pobre, sobre todo, en vitaminas B) bebieron excesivamente; (3) que los ofrecidos una dieta abundante—rica en todos los principios alimenticios esenciales a la rata—no bebieron sino moderadamente; y (4) que los que habían bebido con afán durante el curso del régimen deficitario, *dejaron de beber* al recibir los principios alimenticios que les habían faltado. Se concluye que con la dieta básica las variaciones individuales de la respuesta al alcohol se determinaron por las variaciones metabólicas individuales; que con la dieta marginal la aparición de carencias provocó en todos los animales el deseo de alcohol; que con la dieta abundante no se desarrolló ninguna deficiencia y por eso ningún deseo excesivo de alcohol.

Se examina la aplicabilidad de estos datos al hombre, refiriéndose algunos casos individuales que parecen los confirmen y señalándose una experiencia ahora en curso (Harvard School of Public Health), cuyos resultados preliminares indican que los suplementos nutritivos ocasionan una disminución de la cantidad de alcohol consumido por el hombre, así como por los animales de experimentación.

El autor no quiere excluir del cuadro del alcoholismo los factores psicológicos y sociales, pero cree que el nutritivo, sea primario, sea secundario—nos proporciona una "clave" importante para el mejor conocimiento de tan grave problema.

HYPOVITAMINEMIA A.

*Effect of Vitamin A Administration on Plasma Vitamin A Concentration, Conjunctival Changes, Dark Adaptation and Toad Skin**

By JOHN ESBEN KIRK, M.D.** AND MARGARET CHIEFFI, M.D.†

IN A PREVIOUS study by the present authors[1] a correlation was demonstrated between the plasma vitamin A concentration and the frequency of occurrence of localized conjunctival thickening and toad skin (follicular hyperkeratosis). The ocular lesion observed in the patients with hypovitaminemia A consisted of a raised subconjunctival thickening of triangular shape, having its base at the corneal border and showing some resemblance to pinguecula. No significant correlation was found between the plasma vitamin A concentration and the dark adaptation time.

The present study was undertaken with the purpose of observing the effect of prolonged administration of a dispersion of vitamin A alcohol on various clinical findings, which in the previous investigation by us were shown to have a correlation with hypovitaminemia A. For this reason, a group of individuals who had very low vitamin A plasma concentrations were given a daily supplement of vitamin A for a period of one year, during which time the plasma vitamin A values were followed and the effect on existing conjunctival lesions, blepharo-conjunctivitis, adaptation time and follicular hyperkeratosis recorded. After discontinuation of the vitamin A treatment, the chemical and clinical studies were continued for a seven-month period.

EXPERIMENTAL

The investigation included 23 individuals, 10 men and 13 women, who were inmates or patients of the St. Louis City Infirmary and City Infirmary Hospital. The mean age of the men at the outset of the study was 74 years, and of the women 69 years. None of the individuals suffered from obvious gastrointestinal or hepatic diseases.

The plasma vitamin A concentration of the group was determined in September, 1947, and was found to range between 1 and 13 micrograms per 100 cc. with a mean value of 7.2 micrograms per 100 cc. (s.d. = 4.3). In order to verify the validity of the low plasma vitamin A values of the patients, the determinations were repeated in June 1948, immediately before the commencement of the vitamin A therapy. The analyses showed that the plasma vitamin A concentration had remained low, the values now ranging between 0 and 15 micrograms per 100 cc. with a mean value of 5.1 micrograms per 100 cc. (s.d. = 4.9). During this interval of 9 months the patients received only the ordinary diet of the institution, which

* Vitamin studies in middle-aged and old individuals X

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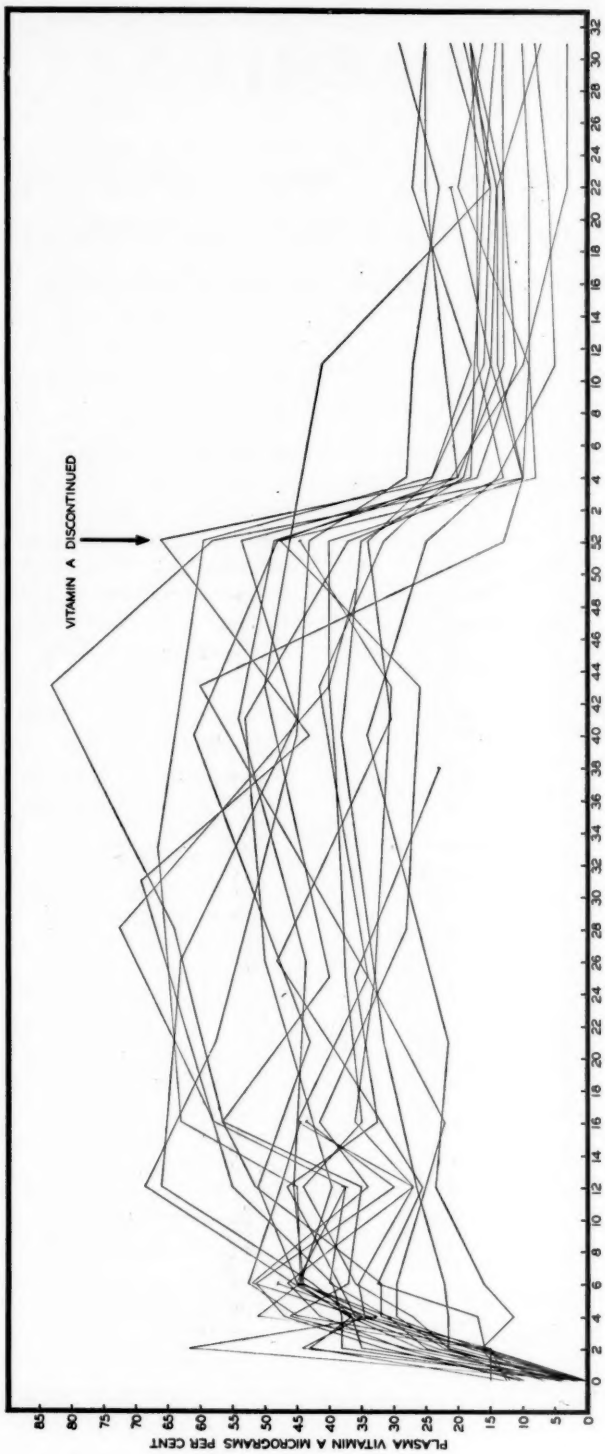
THE EFFECT OF VITAMIN A ADMINISTRATION (30,000 I.U. UNITS DAILY) ON THE PLASMA VITAMIN A CONCENTRATION OF 23 OLD INDIVIDUALS WITH HYPOVITAMINEMIA A
VITAMIN A DISCONTINUED
PLASMA VITAMIN A MICROGRAMS PER CENT
WEEKS

Fig. 1. The effect of vitamin A administration (30,000 I.U. daily) and subsequent discontinuation on the plasma vitamin A concentration in 23 old individuals with hypovitaminemia A.

on direct analysis of the prepared food was found to contain about 10,000 units of vitamin A daily.

Treatment with 30,000 units of vitamin A daily was started on July 1, 1948 and continued until June 30, 1949. The vitamin preparation used was a dispersion of the natural vitamin A acetate which was supplied by Hoffmann-La Roche, Inc. The vitamin was given to the patients in a mixture of grapefruit juice and orange juice each morning, the vitamin preparation being measured off by means of a pipette or measuring cylinder and thoroughly mixed with the fruit juice. The vitamin was administered under supervision by a nurse and was taken willingly by the patients.

The plasma vitamin A determinations were performed as described in detail in a previous publication.[4] The method employed was a modification of the Carr Price procedure recommended by the Association of Vitamin Chemists.[6] The analyses were carried out at intervals of from two to several weeks. All determinations were made in duplicate on fasting blood samples.

Measurement of the dark adaptation time was made by means of a Feldman adaptometer. Since 6 of the 23 patients had to be excluded from the test because of the existence of lenticular opacities or other severe eye lesions, the determination of the adaptation time was performed in only 17 of the 23 subjects. The measurement of the adaptation time and the evaluation of the clinical condition were generally undertaken on the same days the plasma vitamin A level was determined.

Results

Plasma Vitamin A Concentration. The effect of the oral administration of vitamin A on the plasma vitamin A level of the individual patients is presented in Fig. 1, whereas the average vitamin A concentrations for the group are reproduced in Fig. 2. It will be seen from Fig. 1 that the vitamin A plasma value in most of the subjects showed a marked and rapid rise following the commencement of vitamin A administration, and that none of the patients failed to show a definite increase. When the values for the group as a whole are considered (Fig. 2) it will be noted that after 2 weeks of treatment the mean plasma vitamin A value had increased from 5.1 to 26.0 micrograms per 100 cc. During the following month the plasma vitamin A level rose further, to 40.0 micrograms per 100 cc., and 4 months after the beginning of therapy reached a value of 44.5 micrograms per 100 cc., at which level the plasma concentration was maintained during the remaining 8 months of treatment. Following discontinuation of the vitamin A supplementation after 1 year of therapy, the vitamin A plasma concentration dropped sharply, and after 4 weeks had reached a level of 18.7 mi-

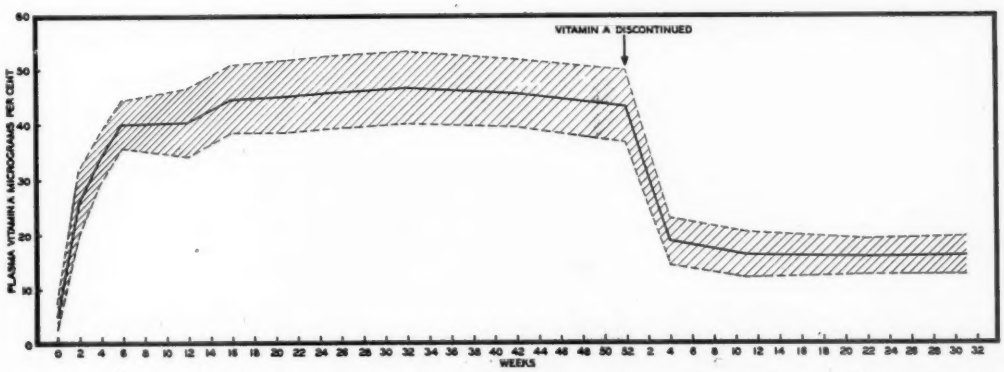

Fig. 2. The effect of vitamin A administration (30,000 I.U. daily) and subsequent discontinuation on the mean plasma vitamin A concentration of 23 old individuals with hypovitaminemia A. (The shaded area represents ±0.5 s.d.)

crograms per 100 cc. A further decrease to about 16 micrograms per 100 cc. occurred during the following weeks, and this level was maintained during the remaining period of observation.

It should be noted that during the 12 months of vitamin administration the number of individuals in the group decreased from 23 to 17 as a result of deaths; in the 7-month period following discontinuation of the therapy the number was reduced further, so that at the end of the 19-month study only 15 individuals remained.

Conjunctival Thickening. The existence of conjunctival thickening was found in 7 of the 23 patients with hypovitaminemia A. As seen from Fig. 3, the treatment with vitamin A was not followed by any immediate noticeable effect on the lesion. Thus, after 4 months of treatment the conjunctival thickening was still present in all the patients. After that time, however, a demonstrable improvement set in, and after 10 months of therapy the lesion had disappeared in the 7 subjects. At the end of the one-year period of treatment 6 of the original 7 patients were still alive.

When the patients were reëxamined 7 months after discontinuation of the vitamin A therapy the conjunctival thickening had recurred in 3 of the 5 individuals and had further appeared in 3 of the other patients in the hypovitaminemia A group.

Blepharo-conjunctivitis. Blepharo-conjunctivitis of varying severity was observed in 16 of the 23 patients included in the study (Fig. 3); among these were the 7 individuals with localized conjunctival thickening. The response of the blepharo-conjunctivitis to the treatment with vitamin A was not rapid, but after 4 months of therapy the lesion had disappeared in 4 of the subjects and at the end of one year's treatment remained in only 2 patients. No local treatment of the conjunctiva or the eyelids was given. Of the 16 patients 14 were alive at the end of the one-year period.

On reëxamination of the patients in January 1950, 7 months after discontinuation of the vitamin A therapy, the blepharo-conjunctivitis was found to persist in the same 2 patients, had recurred in 4 individuals, and had developed in one of the other subjects in the hypovitaminemia A group.

Dark adaptation time. In the previous investigation by the present authors[1] the average dark adaptation time as determined by the Feldman method was found to be 396 seconds for individuals in the age group 60 to 90 years. The mean value of the adaptation time for the 17 patients with hypovitaminemia A included in the present study before the commencement of vitamin A therapy was found to be 434 seconds, a figure which is not significantly different from the average value for individuals of this age ($t = 1.7$).

As will be seen from Fig. 4, the treatment with vitamin A did not result in any notable decrease in the adaptation time for the group as a whole. An analysis of the measurements

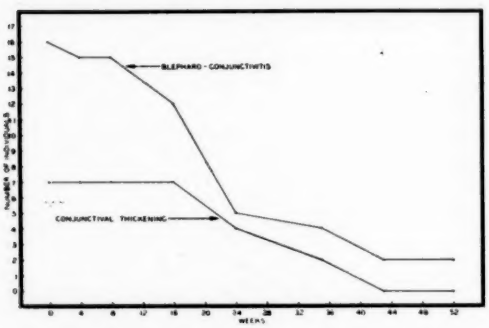

Fig. 3. The effect of vitamin A administration on the incidence of conjunctival thickening and blepharo-conjunctivitis in a group of old individuals with hypovitaminemia A.

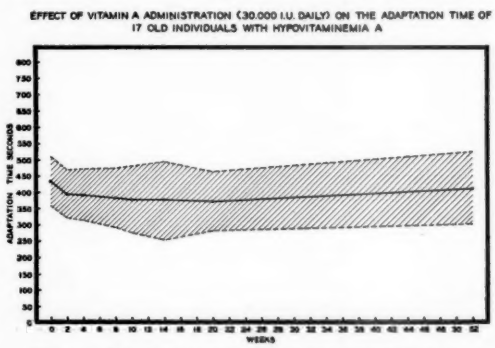
EFFECT OF VITAMIN A ADMINISTRATION (30,000 I.U. DAILY) ON THE ADAPTATION TIME OF 17 OLD INDIVIDUALS WITH HYPOVITAMINEMIA A
ADAPTATION TIME SECONDS
WEEKS

Fig. 4. The effect of vitamin A administration on the mean adaptation time of a group of old individuals with hypovitaminemia A. (The shaded area represents ±0.5 s.d.)

for the individual patients revealed, however, that in 4 of the 17 subjects the vitamin therapy was followed by a significant reduction of the adaptation time values. The data for these 4 patients are given briefly below.

No. 5. Female, 84 years. Original adaptation time 585 seconds; after 42 days' treatment 300 seconds; during the remaining part of the one-year period of vitamin A therapy, 195 seconds.

No. 12. Female, 80 years. Original adaptation time 810 seconds; after 92 days' treatment, 300 seconds; after one year's therapy, 225 seconds.

No. 17. Female, 58 years. Original adaptation time 300 seconds; after 30 days' therapy, 180 seconds; after 75 days' treatment, 90 seconds. The value remained at the latter level during the remaining part of the one-year period of treatment.

No. 22. Female, 59 years. Original adaptation time 390 seconds; after 30 days' treatment, 180 seconds, at which level the adaptation time remained until, after 153 days, the value decreased further to 75 seconds.

The observed effect of the vitamin A therapy in these 4 patients suggests that the prolonged adaptation time was due, at least in part, to vitamin A deficiency.

Five of the 17 patients in the group died during the course of the year.

Toad skin. The effect of the vitamin A administration on the follicular hyperkeratosis in the regions of the forearms, upper arms, thighs and buttocks is presented in Fig. 5, which shows that the skin lesion responded slowly to the vitamin therapy. This was particularly the case with regard to the toad skin on the forearms; thus, after one year's treatment with vitamin A the follicular hyperkeratosis in this area, although frequently somewhat ameliorated, still persisted in 5 of the 8 patients, in whom this sign was present at the onset of the study. In contrast to the toad skin on the forearms, the hyperkeratosis on the upper arms at the end of one year of therapy had disappeared in all the 6 patients having the skin lesion in this region. Of a total number of 13 individuals with toad skin in one or more regions, 10 were alive at the end of the 12-month treatment period.

On reëxamination 7 months after discontinuation of the vitamin A therapy, follicular hyperkeratosis had reappeared on the forearms in 2 patients, and on the upper arm in one patient. Toad skin on the forearms had further appeared in one of the other patients in the hypovitaminemia A group. None of the patients at the time of reëxamination had toad skin on the thighs, but follicular hyperkeratosis in the region of the buttocks was found in the 2 subjects in whom the lesion had not disappeared during the period of vitamin A treatment.

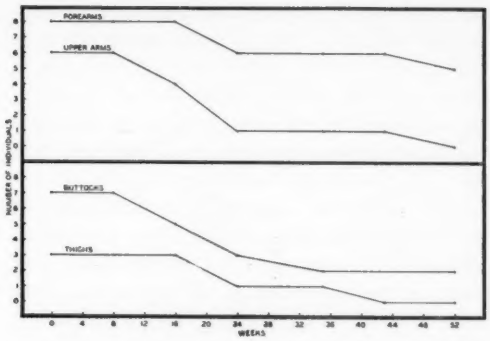

Fig. 5. The effect of vitamin A administration on the incidence of follicular hyperkeratosis in various skin regions in a group of old individuals with hypovitaminemia A.

Discussion

Investigations on the effect of prolonged vitamin A administration on the plasma vitamin A concentration in a large group of adults have not previously been reported. The data presented in the present publication indicate that elderly individuals with hypovitaminemia A are capable of absorbing appreciable amounts of vitamin A when the vitamin is given as a supplement in the form of pure vitamin A dispersion. This finding is in agreement with the results reported by Yiengst and Shock[8] on the basis of vitamin A tolerance curves observed in old subjects.

Robertson and Morgan[7] treated a group of student nurses, several of whom had pinguecula-like elevations of their conjunctivae, with 50,000 units of vitamin A daily for periods up to two years. No effect on the conjunctival lesion was noted. Since plasma vitamin A analyses were not performed at the commencement of the study, it

remains uncertain whether hypovitaminemia A was present. The demonstrated effect in the present investigation of the vitamin A therapy on the localized conjunctival thickening supports the contention of a causal relationship between the vitamin A nutrition and this sign.

The finding in 4 out of 17 individuals of a definite improvement of the dark adaptation following the treatment with vitamin A suggests that impairment of adaptation in some instances is related to A hypovitaminosis. This observation is not necessarily in conflict with the lack of demonstration in a large group of subjects of a significant correlation between the plasma vitamin A level and the dark adaptation time.

Information is lacking in the literature on the effect of vitamin A treatment on follicular hyperkeratosis in patients for whom concomitant plasma vitamin A analyses are available. Several reports, however, have been published on the effect of vitamin A treatment on toad skin in individuals in whom the skin lesion on the basis of the dietary history might be presumed to be caused by a vitamin A deficiency. All were young or middle-aged subjects.

Frazier and Hu[2] in 1931 treated 15 soldiers, between 19 and 33 years of age, who suffered from keratomalacia and showed marked follicular hyperkeratosis, with 15 ml. of cod liver oil daily for periods up to 2 months. The keratotic papules decreased slowly in size but still were present at the end of the observation period. In a later publication (1936) by the same authors[3] on a larger group of patients it is stated that from 2 to 3 months of vitamin A therapy is generally required for the skin to regain its normal appearance.

Youmans and Corlette[9] treated 3 adults, aged 29 to 48 years, with 15 ml. of cod liver oil or 12,000 to 25,000 units of vitamin A concentrate daily. Improvement of the toad skin was noted in from 4 to 8 weeks; disappearance of the lesion in these patients occurred after a total of 8, 18 and 22 weeks of treatment. Finally, in a study by Lehman and Rapaport[5] on a group of children, maximal improvement of the follicular hyperkeratosis was obtained in from 2 to 4 months with a daily dose of 100,000 to 300,000 units of vitamin A.

The observations in the present investigation indicate that in elderly individuals an even longer period of treatment with vitamin A than in children and younger adults is frequently necessary for effecting the disappearance of the toad skin. Since in the present group of patients the plasma vitamin A concentration was found to rise to a normal level within a few weeks after the commencement of peroral vitamin A supplementation it seems reasonable to conclude that the slower response of the skin lesion to vitamin A therapy, in spite of adequate plasma levels, may not have been conditioned by an inadequate supply of vitamin A, but rather by the more advanced age of the patients.

Summary

The effect of vitamin A therapy on the plasma vitamin A concentration, conjunctival lesions, dark adaptation time and toad skin was studied in 23 elderly individuals with hypovitaminemia A. A dose of 30,000 units of natural vitamin A acetate was given daily by mouth for a period of one year.

The treatment resulted in a rise of the mean plasma vitamin A concentration from 5.1 to 44.5 micrograms per 100 cc., at which latter level the plasma vitamin A content was maintained. Following discontinuation of therapy the plasma vitamin A concentration decreased to about 16 micrograms per 100 cc.

A definite beneficial effect on existing localized conjunctival thickening, blepharoconjunctivitis and toad skin was observed, but the response was generally slow.

The adaptation time in 4 out of 17 patients decreased markedly following vitamin A therapy, but in the remaining patients was not influenced significantly.

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Resumen

Hypovitaminemia A. Efecto de la administración de vitamina A sobre la concentración de vitamina A en el plasma, alteraciones conjuntivas, adaptación a la obscuridad e hiperqueratosis

En 23 sujetos de edad avanzada con hipovitaminosis A se ha estudiado el efecto de la vitaminoterapía A sobre: la concentración de vitamina A en el plasma, el tiempo de adaptación a la obscuridad, y la hiperqueratosis ("piel de sapo"). Una dosis de 30,000 unidades por día de vitamina A natural fué administrada oralmente durante un año.

El tratamiento ocasionó un aumento de la concentración media de vitamina A en el plasma de 5.1 a 44.5 microgramos por 100, nivel al que el contenido en vitamina A del plasma se mantenía. Al descontinuar la terapéutica, la concentración de vitamina A en el plasma disminuyó a unos 16 microgramos por 100.

Se observó un efecto beneficioso marcado en los casos de infiltración conjuntiva localizada, de bléfaro-conjuntivitis, y de hiperqueratosis, pero en general la respuesta se produjo con retardo.

En 4 de los 17 pacientes, el tiempo de adaptación a la obscuridad fué considerablemente reducido, pero en los demás no fué notablemente afectado.

The Effects of AMINO ACID DEFICIENCIES *In Man*

By ANTHONY A. ALBANESE, PH.D.*

IT HAS LONG been known that body weight loss and hypoproteinemia constitute the first signs of protein deficiency in man and experimental animals. These results of protein deficiency may arise from a depletion of protein stores as the consequence of disease or of inadequate intake of good quality proteins.

Hypochromic anemia generally is detectable sometime after the onset of the hypoproteinemia and body weight loss. Also, as the protein depots are restored, correction of the anemia usually precedes increases in body weight and total plasma proteins.[1]

Until recently, these changes in man have been assessed primarily in terms of whole proteins; but with increasing knowledge of the biological behavior and composition of various proteins, it has become evident that the overall nutritional value of various proteins is a characteristic of their component parts, namely, the amino acids.

This newer concept led the author and his coworkers some 10 years ago to undertake continuing studies on: (a) the amino acids essential for man; (b) the minimum requirements of each; and (c) the clinical and laboratory manifestations of specific amino acid deficiencies. A partial summary of the results of these investigations has been presented elsewhere.[2] In this report, we shall discuss some of the findings which pertain to clinical nutrition.

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EXPERIMENTAL ANIMALS

It is obvious that the ultimate effects of a protein or amino acid deficiency had to be studied in experimental animals. For this purpose we employed a hybrid strain of albino and hooded Norwegian rats. The effects of protein deficiency were studied by feeding adult animals, for varying periods of time, the protein-free diet shown in Table I. This diet

TABLE I

Composition of Rat Diets

Diets	Control	Protein-Free	Amino Acid Deficient
	gm.	*gm.*	*gm.*
Casein (Sheffield)	15.0	0	0
Deficient Protein Hydrolysate	0	0	15.0*
Brewer's Yeast	4.0	4.0	4.0
Sucrose	15.0	20.0	15.0
Starch	39.3	49.3	39.3
Agar	2.0	2.0	2.0
Crisco	18.0	18.0	18.0
Cod Liver Oil	4.7	4.7	4.7
Salt Mixture (Modified Osborne & Mendel)	2.0	2.0	2.0
TOTAL	100.0	100.0	100.0

* Protein = N × 6.25

contained 0.43 per cent of nitrogen contributed mainly by the presence of yeast, whereas the control diet contained 2.15 per cent of nitrogen. Measurements of blood protein levels in the experimental animals showed that a 20 per cent drop in body weight and total plasma proteins occurred within 40 days. The albumin-globulin ratios fell from an average normal of 2.0 to 1.4 in the same period. A

decline in hemoglobin concentration was observed after 60 or more days of the protein-poor diet.

Nitrogen analyses of tissue shown in Table II disclosed, as previously demonstrated by Addis and his collaborators,[3] that the effect of protein deprivation varies with different tissue. Thus, it will be noted that the greatest effect of the protein-free diet was evidenced in the liver. Indeed, the liver is so sensitive to diet composition that it has been employed as the basis of a rapid bio-assay procedure for the measurement of protein quality.[4] The effects in the carcass and kidney composition are notable chiefly for their variation with duration of the diet. Tissue analysis of depleted animals subsequently fed the control diet showed a return to normal of the liver nitrogen within 20 days.

The principal morphological changes induced by the protein-free diet are indicated in Figure 1. Surprisingly enough, some of the animals survived 185 days on this diet. Edema of the limbs and ascites of the thoracic and abdominal cavities occurred usually after 150 days of the diet.

The effects of the protein-free diet in young and adult animals differ markedly from those produced by diets deficient in one specific amino acid. These are summarized from the observations of others[5] and ourselves[6] in Table III.

TABLE II
Effect of Protein Depletion on Nitrogen Content of Adult Male Rats

Diet	No. of Animals	Days on Diet	Average Initial Weight	Average Weight Change	Carcass	Liver	Kidney
			Gm.	*Gm.*	*Mg. N/Gm.*	*Mg. N/Gm.*	*Mg. N/Gm.*
Control	6	30	320	0	34.4	28.9	27.4
Protein-free	6	40	316	—70	32.3	19.9	32.3
Protein-free	6	80	330	—100	36.5	18.4	20.1
Protein-free	3	120	306	—166	39.7	19.4	24.5

These findings bear the practical implication that a dietary deficiency in one single amino acid, because of the imbalance effects, may produce a greater clinical effect than a low-protein regimen.

With this concept in mind, animals maintained on the protein-free diet were then fed one deficient only in tryptophane. Typical results of these experiments are shown in Figure 2. It will be observed that the weight loss induced in one week by the tryptophane-deficient diet equalled that caused by six weeks of the protein-poor diet. The ocular and

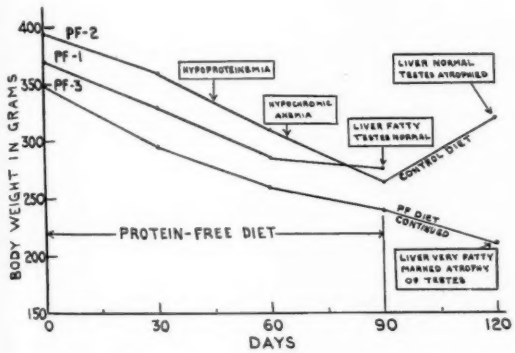

Fig. 1. The effects of protein depletion and repletion in various rat tissues.

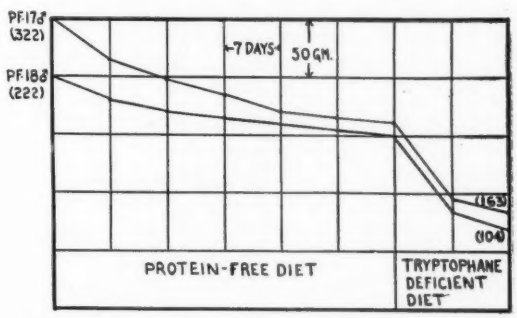

Fig. 2. Effect of tryptophane deficiency on protein-depleted rats. The figure in parentheses indicated initial and final body weight of animals in grams.

dermal tissue lesions observed in the tryptophane-deficient rats were not observed in animals which had been maintained on the protein-free diet for 150 days or more. Tissue analyses of these animals showed that the nitrogen content of the liver was increased by the tryptophane-deficient diet, despite the fact that this tissue had lost none of its fatty and sometimes cirrhotic appearance, and the animals continued to lose weight on the diet.

TABLE III
Pathological Changes in Rats, Caused by Lack of Protein or Specific Amino Acids

Dietary Deficiency	Symptoms*	
	Young Animals†	Mature Animals
Protein	Anemia Hypoproteinemia Edema	Anemia Hypoproteinemia Edema
Tryptophane	Cataracts Poor dentition Alopecia Gastric hyperplasia	Corneal vascularization Alopecia Testicular atrophy Fetal resorption
Lysine	Anemia Sudden death	Anemia Suppressed estrous cycle
Methionine	Anemia Hypoproteinemia Alopecia Fatty liver and cirrhosis	Anemia Hypoproteinemia Fatty liver and cirrhosis
Phenylalanine	Cataracts	
Histidine	Cataracts	
Arginine		Hypospermia
Isoleucine	Anemia Hypoproteinemia	
Threonine	Edema	
Valine	Locomotor dysfunction	
"Unessential amino acids," e.g., glutamic acid, cystine, tyrosine, etc.	Poor growth	

* All changes are reversed when diet is supplemented with missing component.

† All deficiencies and any amino acid imbalance cause corneal vascularization in immature rats.

These observations, albeit made in rats, carry the clinically important suggestion that the diets of patients whose protein stores have been depleted by surgery or protracted illness should contain ample amounts of all the essential amino acids. This can be best achieved by prescribing diets high in animal proteins. Diets constituted principally of vegetable proteins are likely to be lacking in one or more of the essential amino acids—usually tryptophane, lysine, or methionine. A ready and inexpensive source of good quality proteins for rehabilitating such patients is found in those derived from milk.[7]

Human Studies

Young Adults. These investigations[8] were carried out on healthy adults of both sexes between 21 and 25 years of age, who were leading a sedentary life. They were given weighed diets providing approximately 40 calories per kilogram and 0.1 Gm. of nitrogen per kilo per day. These diets were constructed from sugars, starches, fats, and certain fruits and vegetables selected for their low nitrogen content—these last providing about 10 per cent of the daily N intake. The remaining 90 per cent of the protein moiety consisted of a protein hydrolysate rendered deficient in the desired amino acid.

The degradation of complete proteins or hydrolysate by chemical procedures designed to destroy or remove particular amino acids has the advantage of preserving the amino acids in large part in their natural or L-form, and of furnishing the remaining essential and unessential amino acids. This approach in preparing our experimental diets can be criticized on the ground that the chemical manipulations may injure the diet in unknown ways. The deficient protein products were, however, tested on experimental animals with and without supplement of the missing amino acid, and were considered satisfactory only if the supplemented ration restored normal performance in weanling rats.

In all, 30 experiments on 7 amino acid deficiencies were done. The deficient periods were between 3 and 6 weeks in length, and

were preceded and followed by control periods in which the missing amino acid was added to the diet. Nitrogen balance data showed that tryptophane, lysine, and methionine are dietary essentials for the maintenance of N equilibrium, whereas histidine and arginine are not.[2] Concurrent and subsequent studies by Rose[9] confirmed these findings, and further demonstrated that isoleucine, leucine, phenylalanine, valine, and threonine are also needed in the diet for nitrogen balance.

Our attempts to identify the different amino acid deficiency states in terms of blood protein or urinary constituent changes were only partially successful. In general, neither the hemoglobin, albumin, and globulin levels nor the albumin-globin ratios were significantly altered by the deficiencies.

On the other hand, measurements of various nitrogen and sulfur metabolites in the urine resulted in several interesting findings. The tryptophane excretion was found to fall off sharply in the tryptophane-deficient state. However, a tryptophane supplement of 3.0 to 6.0 mg. per kilo sufficed to restore this to normal levels. In the lysine-deficient subjects, it was noted that shortly after the deficient diet was started, there occurred a sharp rise in non-ketonic organic acids in the urine. Subjects fed the histidine-deficient diet showed an abnormal indican reaction. This last finding, however, could not be repeated in subsequent studies.

Urine partition studies of human subjects on cystine- or methionine-deficient diets for a period of 24 days were also made. The nitrogen balance data, as previously mentioned, clearly indicated that methionine is a human dietary essential and that cystine is not. The creatinine output was found to be somewhat reduced in the methionine deficiency.

Other results of the urinary sulfur metabolite analyses are shown in Figure 3. It will be noted that a marked reduction in the excretion of sulfate was induced by the methionine-deficient diet, but not by the cystine-deficient diet. The cystine output diminished progressively, whereas the methionine excretion failed to show any significant changes in both sulfur amino acid deficiencies. A loss of tolerance to the oral administration of either amino acid was also exhibited by the respectively deficient subjects.

It occurred to us that these last findings might lend themselves to the establishment of laboratory diagnostic criteria for the detection of spontaneous deficiencies of these amino acids in man. In subsequent experiences we have found oral methionine load tests helpful in detecting an inadequate intake of this amino acid in several diseases—particularly so in long-standing cases of chronic rheumatic fever in children between the ages of 8–13. In a few of these young patients, a marked gain in body weight occurred with supplementation of their normal diet with 3 to 5 Gm. of L-methionine per day for periods of 2 to 3 months.

In this connection, attention is called to the fact that recent studies have shown that, in descending order, thiocyanate, thiosulfate, sulfite, and hydrosulfite ions interfere with the oxidimetric determination of methionine in biological products.[10] Of these interferents only the thiosulfate ion requires consideration when the measurement is made in human urine. The usual amount of thiosulfate occurring in human specimen introduces a positive error in this measurement of methionine which is roughly equivalent to 20 per cent of the apparent daily output of methionine. These findings account in part for the known discrepancies between the chemical and microbiological procedures. However, they do not in any way invalidate the overall significance of the observations described above.

Infants. Subsequently, studies on the amino acid requirements and effects of amino acid deficiencies in infants were done. The diets employed in these investigations are shown in Table IV. The observations were all made on normal male children who were given the diets in 5 feedings daily. On the basis of changes in rate of weight gain and nitrogen retention induced by fractional supplementation of these diets, we were able to establish the dietary needs for tryptophane, isoleucine, sulfur amino acids, and lysine.

In our continued attempts to establish cri-

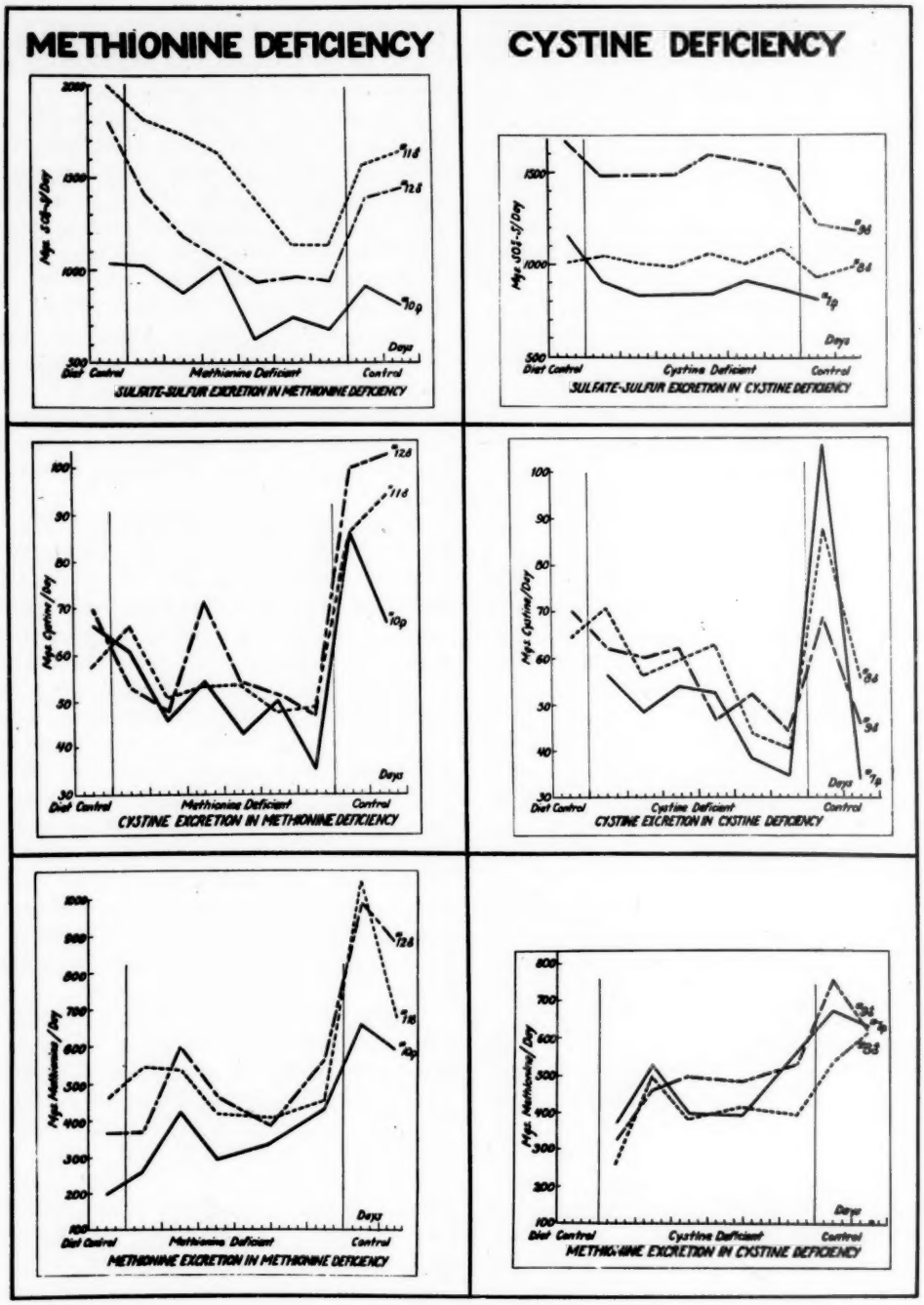

Fig. 3. Sulfur partition of the urine of human subjects on diets poor in methionine and cystine.

TABLE IV
Composition of Diets
(All diets fed at the rate of 100 calories and 3.5 gm. of protein* per kg. per day)

Deficient Diet	Tryptophane	Isoleucine	Sulfur-amino Acids	Lysine
Nitrogen component: Protein products	Acid hydrolyzed casein	Acid hydrolyzed beef hemoglobin	Oxidized casein hydrolysate	Wheat gluten
Basal amino acid supplements	L-cystine	L-tryptophane and L-cystine	L-tryptophane	
Pre- and post-control amino acid supplements	L-tryptophane	L-isoleucine	L-methionine and L-cystine	L-lysine
Carbohydrates	Dextri-maltose No. 2; 9.6 Gm./kg./day Arrowroot starch; 2.3 Gm./kg./day			
Fat	Olive oil; 4.0 Gm./kg./day			
Vitamin Supplements:				
B-vitamins	Brewer's yeast; 1.0 Gm./kg./day			
Vitamins A and D	Oleum percomorphum; 15 drops/day			
Vitamin C	Ascorbic acid; 50 Mg./day			
Water	78cc./kg./day			

* N × 6.25 = grams of protein.

teria for the detection of spontaneous deficiencies of specific amino acids in man, the experimentally induced N losses were characterized by measurements of various nitrogenous and sulfur constituents of the urine and blood protein levels. These results are summarized in Table V.

As might be expected, the biochemical effects of the temporary deficiencies were much more pronounced and characteristic in the infants than in the young adults. The induced urinary changes, which, in part, reflect changes in the metabolic pool, proved most interesting.

The increase in urea output occurring in the tryptophane, sulfur amino acid, and lysine deficiencies may arise from a catabolism of amino acids which are not converted into tissue proteins for lack of one essential amino acid. Apparently, the dismutation of excess amino acids in the isoleucine deficiency is accomplished by a different metabolic path, since this deficiency produced an increase in ammonia output rather than in urea. The rise in urea and ammonia output suggests the functioning of both metabolic mechanisms in the lysine deficiency.

Alterations in the total and specific amino acid excretion were found in all four amino acid deficiencies. The biochemical significance of these observed changes cannot be completely elucidated in our present state of

TABLE V
Biochemical Effects of Specific Amino Acid Deficiencies in Infants*

Deficiency	Trypto-phane	Iso-leucine	Sulfur-amino Acids	Ly-sine
Number of subjects	6	7	9	8
Age range, months	5–12	4–10	4–11	4–8
Days of deficiency required for effects	10	7	10	8
Body weight change	—	—	—	—
Nitrogen retention	—	—	—	—
Urinary constituents:				
Urea nitrogen	+	0	+	+
Ammonia nitrogen	—	+	—	+
Amino nitrogen	—	0/—	—	0
Tryptophane	—	0	—	—
Arginine	+	—	—	—
Histidine	—	—	+	0
Lysine				—
Methionine	+	0	—	+
Cystine	+	—	0/—	+
Phenylalanine	+	—	+	0
Tyrosine		0	0/—	0
Creatinine	0	0	0/—	0
Organic acids	+	0	—	+
Blood proteins:				
Total plasma proteins	—	—	—	0
A/G ratio	0	+	0	0
Hemoglobin	0	0	—	—

* The positive sign (+) denotes an increase of 15 per cent or more above pre- and post-doctoral levels, whereas the negative sign (—) denotes a decrease of 15 per cent or more below pre- and post-control levels. Lesser changes are indicated by 0.

knowledge. Several practical deductions, however, can be made from these results. In the infants, as in the young adults, the deficiency of tryptophane or of the sulfur amino acids causes a decrease in urinary output of these amino acids. The lysine excretion was also found to diminish during the period of dietary lack of this amino acid in the infants; comparable measurements were not made in the young adults for lack of methods at the time of those studies. For the same reason, the output of isoleucine during the isoleucine studies of the infants was not determined.

Thus, in some instances, the urinary level of an amino acid may serve as an index of intake. Further examination of Table V discloses that the changes in urinary metabolite pattern may also serve to indicate the amino acid deficiency which prevails.

The development of chromatographic analyses has greatly simplified this approach to the study of human amino acid deficiencies. Some of the experiences with these techniques have been reported elsewhere.[11] It would appear from these investigations that qualitative and quantitative differences in amino acid levels of the blood and urine exist in children suffering from nephrosis and rheumatic fever. Further applications of the methods being made to problems in protein and amino acid metabolism in man include: (a) the utilization of D-amino acids (b) protein-sparing action of various carbohydrates; and (c) extension of the studies on amino acid requirements of children.

The dietary lack of tryptophane, methionine, and isoleucine was found to so impair the biosynthesis of plasma proteins in infants that a decrease of 20 per cent or more from their normal values was achieved within 10 to 16 days of deficiency.

Much to our surprise, lysine-poor diets were not found to exert this effect. Detailed chemical analyses disclosed that in the dietary absence of lysine, a normal rate of plasma protein biosynthesis was maintained by a substitution of arginine for lysine in the composition of these proteins. This was achieved by a progressive increase in the arginine content of both the albumin and globulin fraction. Reinforcement of the diet with lysine returned the arginine content of the plasma proteins to the normal value within 16 to 21 days. These observations bear the implications that these circulating proteins are completely regenerated within this time interval and that their composition is not immutable.

Comments

Since the process of growth, benign or malignant, can only exist with the predominance of anabolic reactions, it is reasonable to expect that the nutritional support for these biochemical reactions must be quantitatively greater than in the adult phase, in which anabolism and catabolism have reached equilibrium. These considerations explain, in part, the marked chemical differences in the effect of amino acid deficiencies in the infant and the adult. Growth usually involves the formation of new structures, and the hypertrophy and atrophy of others which contain proteins having dissimilar amino acid composition, so that the amino acid requirements of the infant would be qualitatively different from those of the healthy adult.

Evidence for this point can be adduced from the data shown in Table VI. These amino acid values were calculated from the figures

TABLE VI
Amino Acid Requirements of Young Adults and Infants

	Young Adults Rose		Male Infants Albanese	
Amino Acid	Amount	Maintenance* Pattern	Amount	Growth Pattern
	Mg./kilo		Mg./kilo	
Arginine	0	0	126	4.2
Histidine	0	0	63	2.1
Tryptophane	7	1.0	30	1.0
Phenylalanine	31	4.3	169	5.6
Lysine	23	3.2	170	5.6
Threonine	14	1.9	87	2.9
Valine	23	3.2	161	5.4
Methionine	31	4.3	85	2.8
Leucine	31	4.3	425	14.0
Isoleucine	20	2.8	20	3.0

* Growth and maintenance pattern figures obtained by assigning value of unity to tryptophane; in other words, twice as much lysine as tryptophane is required and four times as much leucine.

published by Rose for the young adult and those found by us for the infant by direct and indirect measurements. The pattern of these amino acid requirements was obtained by taking the tryptophane figure as unity.

It is interesting and important to note that the lysine ratio for the infant is almost twice that of the adult. Further examination of this table reveals that the methionine ratio for the adult pattern is significantly higher than that of the infant. From these considerations, it might be deduced that regenerative processes which may be induced in adulthood as the result of shock arising from surgical procedures or acute illness may elicit a partial quantitative and qualitative shift in amino acid needs of the adult to those characteristic of the growth period. Similarly, neoplastic processes can also be expected to cause a shift in amino acid needs of the adult.

Summary

The data presented here support the view that in protein-depleted states a diet poor in one essential amino acid may be more deleterious than one poor in proteins. Evidence has also been presented which supports the concept that certain amino acid deficiencies in man can be identified by changes in amino acid levels in the urine or blood. The development of chromatographic procedures has greatly simplified this approach to the study of nutritional states in health and disease. In the near future we may therefore expect considerable advances in our knowledge of the aberrations of amino acid metabolism in various diseases; and from these advances there may develop a rational system of specific amino acid therapy.

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Resumen

Efectos de las carencias de aminoácidos en el hombre

Los datos aquí presentados sostienen el punto de vista de que en las hipoproteinosis un régimen pobre en un solo ácido aminado esencial puede ser más deletereo que uno que es pobre en proteínas. Se presenta también evidencia en favor del concepto de que ciertos estados de deficiencia de aminoácidos en el hombre pueden ser identificados por alteraciones en el porcentaje de los aminoácidos en la orina o en la sangre. Con el desarrollo de los métodos cromatográficos se ha hecho más accessible el estudio de los estados nutritivos en la salud y en las enfermedades. Nos encontramos, por consecuencia, ante la posibilidad de adelantos considerables en nuestro conocimiento de las aberraciones del metabolismo de los ácidos aminados en las diversas enfermedades; y de ahí puede resultar un sistema racional de terapéutica aminoacídica específica.

The Therapeutic uses of LOW FAT, LOW CHOLESTEROL DIETS

I. Treatment of Essential Familial Xanthomatosis

By FREDERICK URBACH, M.D.,* EUGENE A. HILDRETH, M.D., AND MARIE T. WACKERMAN, B.A.†

SINCE THE introduction of isotope labeling[1] and ultracentrifugal analysis of submicroscopic particles[2] in the study of metabolic processes, there has been a renaissance in the investigation of abnormalities of lipid metabolism. Much of the interest has been centered on studies pertaining to the relationships of cholesterol and other lipids to atherosclerosis, both in the experimental animal and in human beings. Great advances have been made in the elucidation of the intermediary metabolism of steroids,[3] their transport,[4] their etiologic relationships to atherosclerosis,[5] and the genetic transmission of predisposing metabolic traits.[6] Yet the influence of causal therapy on the formation, transport, or excretion of cholesterol and related lipids is still highly disputed.[7,8,9]

Essential familial xanthomatosis is a dominant, familial disease of cholesterol metabolism. Its *forme fruste* is manifested by hypercholesteremia, and its homozygous form by the formation of xanthomatous tumors in the skin, tendons, and rarely in internal organs.[10] Many patients carrying this genetic trait are highly predisposed to the development of atherosclerosis of the coronary and great blood vessels.[11] Some investigators believe that the hypercholesteremia which invariably accompanies this metabolic abnormality is causally related to the high incidence of premature, severe atherosclerosis—the most common cause of death in patients with essential familial xanthomatosis. Most children and adolescents dying of coronary occlusion have been found to carry this familial trait.[12,13]

The association of hypercholesteremia with essential familial xanthomatosis led early to the belief that dietary restriction of lipids could be used as a therapeutic measure.[14] No attempt will be made here to review again the voluminous literature pertaining to the effects of lipid restriction on hypercholesteremia, atherosclerosis, or xanthomatosis.[4,5,8,15,16] From the reported data several conclusions may be drawn:

1. Restriction of dietary cholesterol alone has no significant effect on human serum cholesterol levels.

2. Restriction of dietary cholesterol and of animal fats has only an occasional—and then not very dramatic—effect on serum cholesterol levels, particularly if the vegetable fat intake is increased.

3. Restriction of dietary cholesterol and of

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all fat (animal and vegetable) seems to have a profound effect on serum cholesterol levels of normal and hypercholesteremic subjects, provided that the total daily fat intake is limited to 25 Gm. or less.

4. Experimentally induced atherosclerosis in animals, and perhaps even spontaneous human atherosclerosis, seems to be reversible, at least to a certain degree.

It is therefore interesting to note that observers reporting lowering of hypercholesteremia and involution of xanthomatous cutaneous lesions restricted total fat,[14,17,21] while those reporting negative or poor results fed their patients significant amounts of vegetable fat.[6,11,22]

To evaluate the effects of a low fat, low cholesterol regimen, we placed patients with proved essential familial xanthomatosis on a diet containing approximately 20 Gm. total fat and 100 mg. cholesterol per day. Serial determinations of serum lipids, electrocardiograms (ECG), ballistocardiograms (BCG), and careful physical examinations were performed at regular intervals. The results of these investigations are reported here.

Material and Methods

Nine patients with essential familial xanthomatosis were studied. In each the diagnosis was based on clinical evidence of cutaneous or tendon xanthomata or both, confirmed by biopsy. All had varying degrees of hypercholesteremia with clear, or only slightly, turbid serum. Basal metabolic rates (BMR), glucose tolerance, liver and renal function tests were normal in all patients. After baseline studies had been completed, all patients were placed on the low fat, low cholesterol diet described by Hildreth *et al.*[23] The only modification was the addition of numerous recipes for fat free and low fat dishes and adjustment to 20 Gm. total fat intake per day. The patients received no other therapy except for daily supplements of synthetic vitamins A and D.* Since all studies were performed on an out-patient basis, close check was kept on the actual fat intake by asking patients to record in detail their entire food intake for one day out of each week. These records were examined by a trained dietitian and the actual fat intake calculated. If more than 20 Gm. total fat had been ingested during any one period, the patients were advised to restrict their diet further.

Cholesterol was determined by a method developed by Dr. John Reinhold in the Pepper Laboratory of the University Hospital.†,[24] The results were compared periodically with those obtained by the method of Sperry and Webb.[25] Close agreement was consistently obtained. Total lipids were measured by the turbidimetric method of Kunkel *et al.*[26] and phospholipid by the method of Zilversmidt and Davis.[27]

ECG, cardiac fluoroscopy, and BCG were performed every three to four months during the course of the study. Peripheral circulation was checked every three months in a warm room.

The nine patients studied may be divided into two groups.

Group A (Table I) consisted of six patients with cutaneous lesions but who had no tendon lesions. One of these had xanthelasma palpebrarum as the only cutaneous symptom. Three had mild to moderate angina pectoris and two peripheral vascular occlusive disease.

Group B (Table II) consisted of three patients with tendon and cutaneous xanthomata. In all, onset of the disease dated back to childhood or early adolescence. One had severe angina pectoris and advanced myocardial damage.

The duration of adherence to the low fat, low cholesterol diet varied from eight months to seven years.

The individual case histories are appended (page 60).

* We are indebted to Dr. Harvey Blank of Squibb and Sons, Inc., and Mr. H. L. Ferrier of Wyeth, Inc., for generous supplies of synthetic vitamin A and D preparations.

† An alcohol-ether extract of serum is evaporated to dryness, taken up in chloroform, treated with a 10:1 mixture of acetic anhydride and sulfuric acid. After color is developed in a waterbath at 38° C. for ten minutes, readings are taken in an Evelyn colorimeter. Cholesterol Stearate is used as standard.

Results

All patients showed a significant fall of serum cholesterol levels while on the diet (Tables I and II). Total and ester cholesterol and total turbidimetric lipids fell proportionately, so that the ratios remained relatively constant. In the few patients in whom serial phospholipid determinations were made, these too varied proportionately. The response of serum lipids was much more dramatic in patients without tendon lesions; the lipids reached normal or near normal levels in two to four months. An increase of fat in the diet usually caused a rise of serum lipids. This response was much more pronounced in Group B, where addition of as little as 10 Gm. of fat daily resulted in considerable elevation of serum lipids. After an initial weight loss of 6–10 pounds, all patients maintained their body weight while on the diet.

All patients in Group A showed significant to complete involution of skin lesions. (Figures 1 to 4.) Involution began three to four months after initiation of the 20 Gm. fat diet. Interestingly enough, when greater fat ingestion brought about a recrudescence of hypercholesteremia to pretherapy levels for considerable periods of time, the skin lesions did not recur. (Patients R. B. and J. B.) Over a seven to fourteen months' period, no effect was noted on the extensive tendon and skin lesions of the patients in Group B. One patient (R. K.) actually developed tendon lesions while under observation, in spite of adherence to the diet. None of these patients reached even near normal serum cholesterol levels.

Four of the patients had angina pectoris and two had occlusive peripheral vascular disease. Half the patients in our small group had atherosclerotic symptoms. In two patients the vascular symptoms began in adolescence.

In patient H. M., angina disappeared completely in three to four months. Over a twelve-month period the BCG, which initially showed changes typical of coronary artery disease, improved very considerably. Prior to therapy the H waves equaled or were greater than J waves in expiration; the I wave was at baseline or above in expiration, and tiny and deformed. Improvement was reflected in deeper I waves, reaching below baseline, and in less deformity and larger J waves. The cardiac output, as calculated from the BCG, increased.

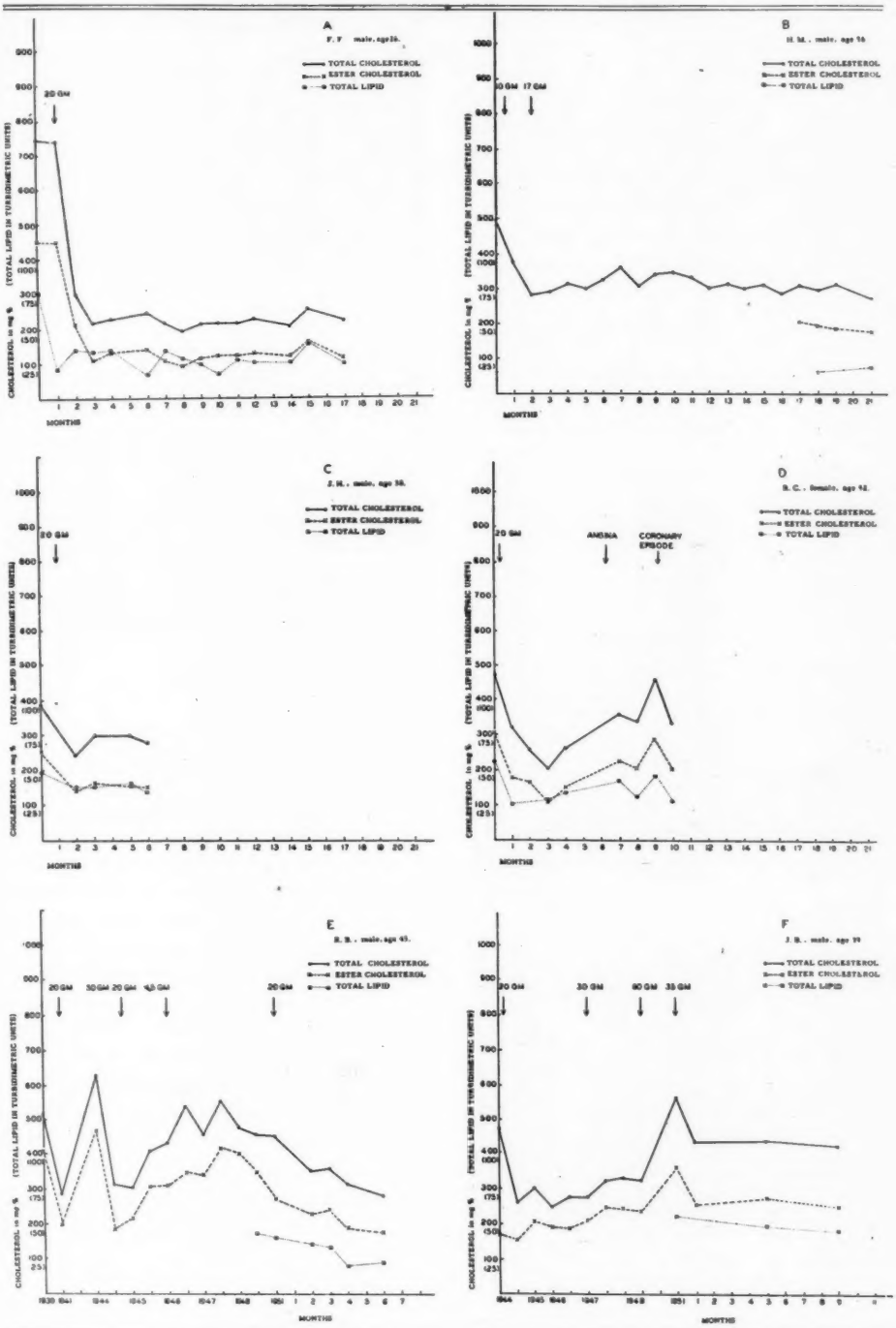
Patient L, W., who had had severe angina pectoris since age 27, showed considerable symptomatic improvement—evidenced by less frequent attacks and decreased nitroglycerine requirement. The BCG, which initially showed marked hypokinemia, subnormal circulation, I-J and J-K notching and abnormal form, improved, as evidenced by increase in the calculated cardiac output, I waves reaching below baseline, and return of form to normal. Shortly before the patient died from acute myocardial infarction, there was some deterioration of the BCG (increase of H waves in size, equaling that of J waves in expiration). (Figure 5)

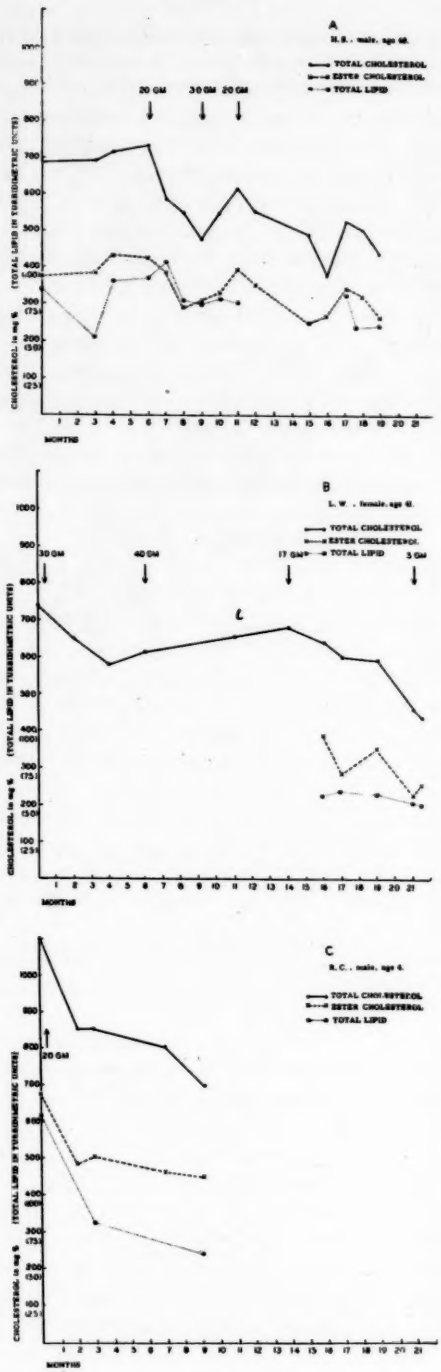
Patient R. C. had moderately severe angina pectoris and normal ECG and BCG. On the low fat diet her serum cholesterol fell to normal, and cutaneous lesions improved greatly. After four months of therapy, even though the diet remained essentially the same, the serum cholesterol gradually rose to almost pretreatment levels. At the height of the hypercholesteremia the patient developed severe angina and a minor coronary occlusion. Simultaneously the BCG showed decreased cardiac output in the presence of normal form. Following this episode, the serum cholesterol level again began to fall. It is interesting to speculate whether the rise in serum cholesterol from apparently basal conditions was causally related to the coronary episode, particularly since it has been reported that serum cholesterol rises during acute coronary attacks and drops to previous levels during recovery.[28]

Patient J. B. has been followed intermittently for seven years. After an initial drop in serum cholesterol and disappearance of cutaneous lesions, in recent years he has not adhered well to the prescribed diet. Since the serum cholesterol has remained at about 400 mg. per 100 cc. he has developed mild angina. The BCG was normal at rest, but smoking was followed by changes typical of coronary disease.

TABLE I

Effect of low fat, low cholesterol diet on the serum lipids of patients with essential familial xanthomatosis having only cutaneous lesions (Group A)





Discussion

Our results indicate that a 20 Gm. fat, low cholesterol regimen profoundly affects the natural course of essential familial xanthomatosis. For discussion purposes, this metabolic disorder may be considered to have three main manifestations: hypercholesteremia, xanthomatous tumors, and associated atherosclerosis.

I. Effect of Low Fat, Low Cholesterol Diet on the Hypercholesteremia of Essential Familial Xanthomatosis

It has been well established that it is possible to lower serum cholesterol levels by drastic restriction of both total fat and cholesterol in the diet.[4,8,9,14,16-21,23,29-36] Our findings in patients considered to have abnormalities of the cholesterol metabolism confirm this observation. The mechanism responsible for this effect is not clear. It has been shown by tracer studies that nearly all tissues can synthesize cholesterol from short chain hydrocarbon fragments, which may be derived from fats, carbohydrates or proteins.[3] It seems unlikely that the relatively rapid effects observed by us are due to interference with cholesterol synthesis, particularly in the presence of an easily accessible pool of stored fat. Undoubtedly, restriction of dietary lipids has a considerable effect on fat transport, as indicated by the studies of Gofman and associates on the effects of low fat diets on lipoprotein complexes.[36] It is likely that dietary lipid restriction lowers serum cholesterol by affecting cholesterol absorption and excretion. It is known that crystalline cholesterol is not absorbed from the gastrointestinal tract unless esterified and incorporated into a phospholipid-fatty acid complex.[37] Relatively large amounts of cholesterol are excreted into the intestinal tract by way of the bile[38] and directly through the intestinal mucosa.[39] Most of this cholesterol is ordinarily reabsorbed,

← Table II

Effect of low fat, low cholesterol diet on the serum lipids of patients with essential familial xanthomatosis having both skin and tendon lesions (Group B)

Fig. 1a. Patient F. F. before therapy.

Fig. 1b. Patient F. F. after eight months on low fat, low cholesterol diet.

only a fraction being changed to coprosterol or open chain acids and excreted with the feces.[40] In the absence of dietary fat, the endogenously formed cholesterol excreted into the gastrointestinal tract is probably not reabsorbed and thus is lost to the body. It seems likely that at least part of the beneficial effect of low lipid diets on serum cholesterol levels is due to lack of reabsorption of endogenous excreted sterol. Some preliminary balance experiments in normal subjects on normal and low fat diets seem to confirm this contention.[41,42] This would explain the necessity for restriction of vegetable as well as animal fat, since esterification and transport of cholesterol across the intestinal mucosa may proceed with either.

II. Effect of Low Fat, Low Cholesterol Diet on Xanthomatous Tumors

There appears to be a considerable difference in the rate of reabsorption of xanthomatous lesions between the patients in Groups A and B. The difference is strikingly associated with the presence or absence of tendon involvement; however, it must be remembered that our patients with tendon xanthomata developed their disease early in life, had much more extensive involvement, and probably represent an extreme of metabolic abnormality (evidenced by the very slow reduction of hypercholesteremia on the restricted diet). Furthermore, it is probable that the cholesterol deposits are removed by vascular pathways. Since older xanthomata and all tendon lesions show a great deal of fibrosis and consequently have poor circulation, it is reasonable to assume that such lesions will disappear only gradually. It is likely that as more such patients are studied, reduction in size of tendon

Fig. 2a. Patient F. F. before therapy.

Fig. 2b. Patient F. F. after eight months on low fat, low cholesterol diet.

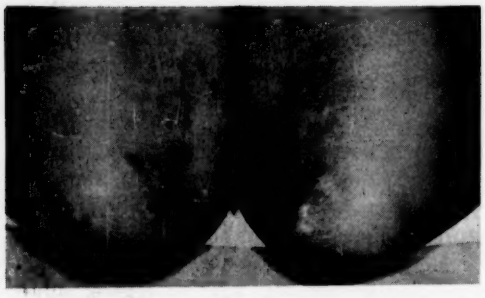


Fig. 3a. Patient R. C. before therapy.

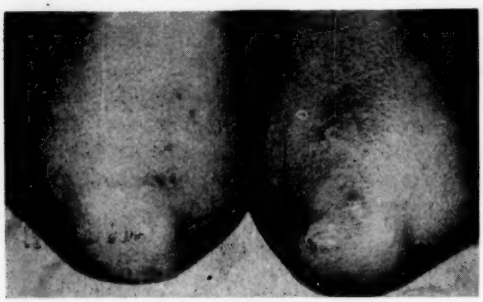


Fig. 3b. Patient R. C. after seven months on low fat, low cholesterol diet.

Fig. 4a. Patient R. B. before therapy.

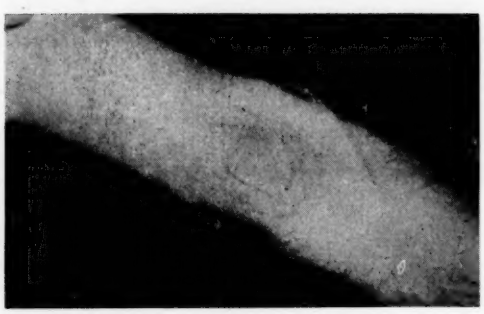


Fig. 4b. Patient R. B. after seven years on low fat, low cholesterol diet.

lesions will be observed, since at least one case has been reported in which tendon xanthomata disappeared on a dietary regimen similar to ours.[18] The only patient in the entire group in whom tendon lesions actually were first observed and cutaneous lesions increased in size in spite of the low fat diet was a child whose extreme hypercholesteremia was only slightly affected by lipid restriction (patient R. K.).

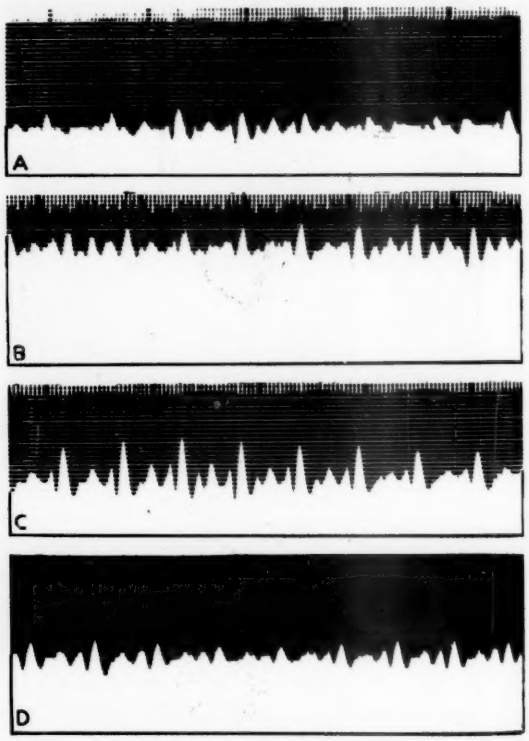


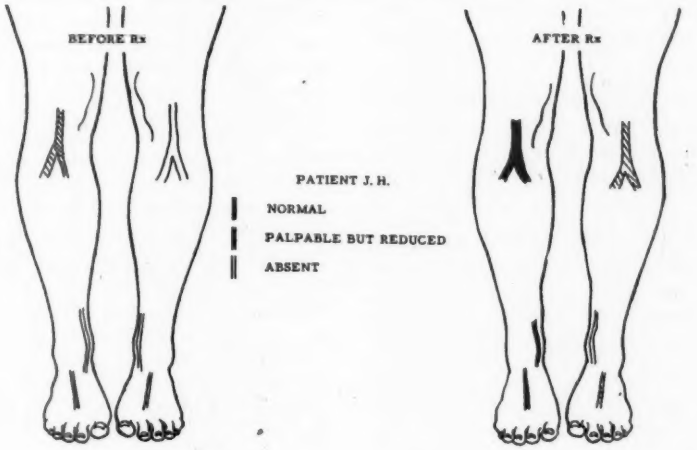
Fig. 5. Effect of low fat, low cholesterol diet on the ballistocardiogram of patient L. W. (*A*) Before therapy. (*B*) After 6 months on 30-Gm. fat diet. (*C*) After 18 months on low fat, low cholesterol diet. (*D*) One week prior to death. For interpretation of changes see text.

III. Effect of Low Fat, Low Cholesterol Diet on Associated Atherosclerosis

All patients with angina pectoris showed at least temporary improvement. Initially abnormal BCG improved greatly during dietary therapy. To our knowledge, progressive improvement of BCG in patients with angina pectoris has not been reported previously.

TABLE III

Effect of low fat, low cholesterol diet on the peripheral vascular sclerosis of a patient with essential familial xanthomatosis



RIGHT POSTERIOR TIBIAL , AND LEFT POPLITEAL, ANTERIOR AND POSTERIOR TIBIAL PULSES ABSENT. OSCILLATIONS MARKEDLY REDUCED IN BOTH LEGS.

ALL PULSES EASILY PALPABLE ON THE RIGHT. LEFT POSTERIOR TIBIAL PULSE ABSENT. OTHER PULSES ON LEFT DIMINISHED BUT PALPABLE. OSCILLATIONS NORMAL ON THE RIGHT. IMPROVED ON THE LEFT.

IN ONE YEAR, THE CLINICAL SYMPTOMS OF INTERMITTENT CLAUDICATION HAVE IMPROVED 50%. PERCEPTIBLE OBJECTIVE IMPROVEMENT IS EVIDENCED BY REAPPEARANCE OF PREVIOUSLY ABSENT PERIPHERAL PULSES AND INCREASE IN AMPLITUDE OF OSCILLATIONS AT THE ANKLE. ALL MEASUREMENTS WERE PERFORMED AT REST AND DURING FULL THERMAL VASODILATATION.

The two patients who had peripheral vascular occlusive disease have shown remarkable improvement, as evidenced by disappearance or considerable lessening of intermittent claudication and reappearance of previously non-palpable leg pulses. (Table III.)

The objective improvement of symptoms known to be due to atherosclerotic disease of important blood vessels suggests the possibility that atheromatous deposits in humans may be resorbed under the influence of a low fat, low cholesterol diet.

Summary

Nine patients with proved essential familial xanthomatosis were placed on a low fat, low cholesterol diet and followed for periods ranging from eight months to seven years. The diet was adjusted to contain approximately 20 Gm. total fat and 100 mg. cholesterol daily.

All patients showed a significant fall in serum cholesterol levels while adhering to the diet. In the patients without tendon lesions the serum cholesterol returned to normal or near normal limits. In those with tendon xanthomata the response was much slower, less dramatic, and incomplete.

Cutaneous xanthomata, when not accompanied by tendon tumors, involuted partially or completely. Reduction in size of the lesions

began two or three months after initiation of therapy. No change was noted in those patients having both tendon and cutaneous lesions. One child developed tendon lesions while on the diet.

All patients with angina pectoris improved clinically.

Progressive improvement of ballistocardiographic pattern was seen in two patients and in one the record deteriorated concomitant with what was probably a small infarct. Reappearance of pulsation in previously nonpalpable leg vessels and lessening of intermittent claudication observed in two patients indicates improvement in major peripheral arterial circulation. It thus appears that adherence to a low fat, low cholesterol diet can produce amelioration of atherosclerotic symptoms, perhaps by promoting resorption of atheromatous deposits.

Case Histories

Group A (see Table I)

F. F., 24-year-old white male movie projector operator, was first seen on June 7, 1950 complaining of yellowish cutaneous nodules of eight months' duration. In November 1949 the patient had first noted gradual appearance of yellowish nodules and plaques in the creases of both palms. Three months later, similar lesions appeared on both buttocks, and then over the knees and heels. Except for local discomfort due to pressure on nodules, there were no untoward symptoms. The patient had no past history of serious disease. His father suffers from thromboangitis obliterans and arteriosclerotic heart disease. There was no family history of cutaneous xanthomatosis.

General physical examination, including cardiac fluoroscopy, ECG, and BCG was normal. The cutaneous lesions consisted of oval nodules and flat plaques of yellowish hue, embedded in the upper corium and epidermis, movable over deeper tissues and located in the flexion creases of both palms, the soft tissues of the fingers, over both buttocks, knees, and Achilles tendons. There was no palpable tendon involvement. Biopsy of a nodule from the buttock was reported as xanthoma. Laboratory studies showed a negative urinalysis, basal metabolic rate +2, fasting blood sugar of 78 mg., total cholesterol 754 mg., ester cholesterol 459 mg. per 100 cc., total turbidimetric lipids 75.4 Kunkel units (KU), and normal liver function tests.

The patient was placed at first on a diet limited to about 50 Gm. of fat daily, on which over a two-month period there was no change in serum cholesterol level or skin lesions. On October 16, 1950 he was started on the 20 Gm. fat, low cholesterol diet. By November 27, 1950 the serum cholesterol level had fallen to 296 mg. per 100 cc. and there was some involution of skin lesions. By January 2, 1951 the serum cholesterol was normal (211 mg. per 100 cc.) and the skin lesions had improved strikingly. In March 1951 all lesions on palms, knees, and heels had disappeared, and the buttocks were 75 per cent improved. The serum cholesterol level has remained within normal limits and the patient has felt entirely well. He lost a total of 10 lb. early in the course of therapy but has maintained his body weight for the past twelve months. (Table IA, Figures 1a and 1b and 2a and 2b.)

H. M., 55-year-old white male clerk, was first seen in February of 1950 complaining of poor circulation in the left leg. The patient was apparently entirely well until September 1949 when he first noted pain in the left calf on walking two to three blocks. There was no history of previous vascular disease or other serious illness. In the two months prior to admission, the leg pain had become progressively more easy to produce. Three days prior to admission, numbness was noted in the left leg, less marked if the foot was dependent. The patient had xanthelasma palpebrarum for many years. General physical examination revealed only a soft systolic murmur at the apex of the heart and over the aortic area. Cardiac fluoroscopy and ECG were normal. The pulses in both wrists were palpable. No pulses could be felt below the femoral artery in the left leg, and the pulses in the right dorsalis pedis and popliteal arteries were absent. Laboratory studies showed a fasting blood sugar of 97 mg. per 100 cc., normal glucose tolerance and liver function tests and a serum cholesterol level of 495 mg. per 100 cc. The patient was started on Buerger's exercises, priscoline, and whiskey and placed on the low fat diet. In July 1950 he had two typical anginal attacks. The BCG was distinctly abnormal, showing H waves equal to or greater than J waves in expiration; the I waves were at the baseline or below in expiration and were tiny and deformed. The patient has adhered faithfully to the 20 Gm. fat, low cholesterol diet, and in March 1952 anginal attacks had completely disappeared, claudication was minimal, all pulses of the right foot were again palpable and no objective change had taken place in the vessels of the left foot.

The BCG improved considerably, I waves becoming deeper and reaching below the baseline and J waves becoming less deformed and larger. The calculated cardiac output increased significantly. The serum cholesterol level fell to 281 mg. total and 165 mg. esters per 100 cc. The eyelid xanthelasmata have involuted about 20 per cent. (Table IB.)

J. H., 30-year-old white male machinist, was first seen on April 3, 1950 complaining of tender nodules over the elbows and knees. Two years prior to ad-

mission he first noted two small yellow nodules in the skin over the left olecranon process. Subsequently more of these nodules appeared at the same site and over the opposite elbow. A similar lesion recently appeared over the right knee. The patient came to the clinic because the nodules were painful on pressure. Prior to admission, fasting blood sugar, blood count, serologic tests for syphilis and chest x-ray had been normal. For nine months prior to admission, patient had noted cramplike pain in the calves, occurring after walking one or two blocks at regular gait, and relieved by rest. The pain was always more severe in the left than in the right calf. The patient smoked 10–15 cigarettes per day. There was no history of diabetes mellitus, cardiac disease, or xanthomata in his immediate family.

General physical examination revealed no abnormalities of the heart, lungs, or central nervous system. The ECG, BCG, and cardiac fluoroscopy were within normal limits. The left popliteal, posterior tibial and dorsalis pedis pulses were not palpable. The right dorsalis pedis artery was not palpable, the other pulses of the right foot being reduced in strength. Blanching time with legs elevated was increased on the left and normal on the right. Flushing time was delayed on the left side only. Oscillations were reduced at both ankles. The toes were cool. The cutaneous lesions consisted of groups of discrete, yellowish, firm nodules, 2–6 mm. in diameter, located in the skin overlying both elbows and the right knee, surrounded by a faint erythematous halo. There was no palpable tendon involvement.

Laboratory studies showed a fasting blood sugar of 102 mg., a serum cholesterol level of 385 mg. with 250 mg. esters per 100 cc., total turbidimetric lipids 49.6 KU, normal liver function tests, BMR -2 and negative urinalysis. The patient was placed on a diet containing 50 Gm. of vegetable fat and given three grains of thyroid substance daily. On this regimen there was no significant change in serum cholesterol levels or skin lesions over a six-month period.

In January 1951 the patient was placed on the 20 Gm. fat, low cholesterol diet. In the next twelve months the skin lesions disappeared almost completely and the serum cholesterol fell to 300 mg. per 100 cc. The most remarkable changes took place in the patient's peripheral vascular symptoms. One year after initial examination and eight months after institution of the rigid low fat diet, his claudication had improved 50 per cent. Reëxamination of leg vessels showed the left dorsalis pedis and popliteal pulses to be palpable, although weak, and the left posterior tibial pulse to be absent. All pulses in the right leg were palpable and strong. Blanching time was still slightly accelerated on the left, flushing time normal and equal in both legs. It was the impression of the peripheral vascular consultant (Dr. Hugh Montgomery) that there had been definite objective improvement in the peripheral vessels since the last examination one year earlier. (Tables IC and III.)

R. C., 52-year-old colored housewife, was admitted to the Hospital of the University of Pennsylvania in-patient service in September 1950 because of shortness of breath on exertion and precordial pain. The patient was generally in good health until 1948 except for hunger pains in the midabdomen, not related to food, occasionally accompanied by nausea and vomiting, present for twelve years. In 1948 she developed small yellowish-brown nodules over both knees and elbows. In 1949 typical xanthelasmata appeared on the inner canthi of both lids. In January of 1949 the patient developed shortness of breath and constricting chest pain on exertion, occasionally accompanied by sharp precordial pain radiating to the back. In December 1949 the shortness of breath and chest pain appeared even after mild exertion. Hospitalization at that time revealed chronic gastritis. The ECG was normal.

The patient's father and brother died of arteriosclerotic heart disease. Eight other siblings and one child were living and well. There was no family history of xanthoma, xanthelasma, or diabetes mellitus.

General physical examination showed no abnormalities of heart, lungs or central nervous system. Gastrointestinal series revealed chronic gastritis, and diverticulosis of the duodenum, terminal ileum and colon. There were numerous small, raised, yellowish-brown nodules located in the skin over both elbows and knees, varying in diameter from 3 to 6 mm. There were no tendon lesions.

Laboratory studies showed a serum cholesterol level of 474 mg. per 100 cc., with 307 mg. esters, total turbidimetric lipids of 57.1 KU, phospholipid of 15.5 mg. P per 100 cc., fasting blood sugar of 91 mg. per 100 cc., normal liver function tests, and negative serological tests for syphilis (STS). The ECG and BCG were normal. Biopsy of the skin lesion was reported as xanthoma tuberosum.

The patient was started on a 60 Gm. fat diet in September 1950. Over a seven-month period on this regimen there was some decrease in the frequency of the anginal attacks, but no change in serum cholesterol levels or skin lesions. In March 1951 the patient was placed on the 20 Gm. fat, low cholesterol diet. During the next five months the serum cholesterol level fell to 215 mg. per 100 cc. and phospholipids diminished to 10.1 mg. P per 100 cc. Concomitantly, the lesions decreased 75 per cent in size and the angina improved considerably. There was no change in the previously normal ECG and BCG. From September to December 1951 the patient's serum cholesterol level gradually rose, even though there had been no change in her diet. At the same time the anginal attacks became more frequent. In January 1952 the patient suddenly developed a severe attack of precordial pain, lasting several hours, not improved by nitroglycerine. ECG taken five days later showed inversion of the T waves in all limb

leads. The cholesterol level had risen to 435 mg. per cent and the BCG, while not definitely abnormal, showed some decrease in the calculated cardiac output. In the next six weeks the patient improved considerably on semi-bedrest, and the serum cholesterol level fell to 334 mg. per 100 cc. It was the impression of the attending cardiologist (Dr. Peter Kuo) that the patient had sustained an occlusion of a small coronary artery. (Table ID and Figures 3a and 3b.)

R. B., 45-year-old white male clerk, was first seen in 1939 by Dr. Erich Urbach. Early in 1939, after almost a full year on a ketogenic diet prescribed for the control of idiopathic epilepsy, patient began to notice yellowish streaks and plaques in the flexion creases of the palms of the hands, and over the elbows. These increased in number and size until the ketogenic diet was discontinued. Except for recurrent major epileptic seizures, controlled by sedation and ketogenic diet, he had always been well. His father died at age 58 of heart disease, and one brother had similar skin lesions.

At the time of admission, there were bright yellow infiltrated, slightly raised plaques in the flexion creases of both hands, a similar nodule was present between the fourth and fifth toes, and there were large yellowish masses over both elbows. There was a typical xanthelasma on the inner canthus of the right upper eyelid. The general physical examination and ECG were negative.

Laboratory examinations showed fasting blood sugar of 82 mg. per cent, serology negative, glucose tolerance normal, cerebrospinal fluid (CSF) within normal limits, total cholesterol 520 mg. per 100 cc. Biopsy was reported as xanthoma tuberosum. From 1939 to 1946 the patient was subjected to a series of experiments consisting of varying the fat, protein, and carbohydrate content of the diet. It was found that a low (20 Gm.) fat, low carbohydrate diet caused rapid reduction of cholesterol levels to normal, and complete disappearance of cutaneous lesions. Detailed results on this patient and his brother (J. B.) were reported by Dr. Erich Urbach previously.[2] From 1946 to 1951 the patient did not adhere well to the restricted diet, with the result that his serum cholesterol level rose to 456 mg. per 100 cc. In spite of this prolonged (5-year) lapse of dietary fat restriction, there was no recurrence of cutaneous lesions. In March 1951 he was placed on the 20 Gm. fat diet. At that time his serum cholesterol level was 454 mg. total cholesterol with 279 mg. esters per 100 cc., total turbidimetric lipids 45.8 KU, phospholipids 13.7 mg. P per 100 cc., liver function tests normal. In the following eight months his serum cholesterol level fell to 271 mg. per 100 cc., and he felt entirely well. It is interesting to note that, although a BCG taken in April 1951 was normal, the inhalation of the smoke of one cigarette was able to change the BCG pattern to that usually associated with coronary disease. (Table IE and Figures 4a and 4b.)

J. B., 39-year-old white male contractor, was first seen in 1944, by Dr. Erich Urbach. The patient had noted the gradual development of yellowish nodules of the skin overlying both elbows as early as 1942. The exact onset of lesions was not known. From 1940 to 1944 he had recurrent furunculosis of the neck and arms. Otherwise he had never been seriously ill. His brother (R. B.) had been under study for some years because of xanthomata. His father had died at age 58 of cardiac disease. There was no family history of diabetes mellitus. On admission, the patient showed many small distinct yellowish nodules in the skin overlying both elbows. There were a few purplish nodules present on the back of both thighs presenting a yellowish tinge on pressure. On the dorsal surface of both big toes were many brownish-yellow lesions. The flexion creases of both hands were distinctly yellow. General physical examination and ECG were normal. Biopsy of skin lesion was reported as xanthoma tuberosum.

Laboratory examinations showed a fasting blood sugar of 107 mg. per cent, total cholesterol 440 mg. with 165 mg. esters per 100 cc. This patient, like his brother, was treated with a low fat (20 Gm.), low carbohydrate diet, and in the period from 1944 to 1946 the serum cholesterol level fell to 286 mg. total and 210 mg. ester cholesterol per 100 cc. All cutaneous lesions disappeared. From 1946 to 1951 this patient gradually relaxed his dietary restrictions, with resulting rise in serum cholesterol. He was seen again in April 1951, at which time the serum cholesterol level was 558 mg., ester cholesterol 372 mg. per 100 cc. total turbidimetric lipids 53.6 KU, phospholipids 14.9 mg. P. per 100 cc. and liver function tests normal. The patient failed to adhere to the 20 Gm. fat diet. According to our calculations, he has been ingesting about 30–40 Gm. of fat per day. On this regimen his serum cholesterol level has dropped to 437 mg. total and 255 mg. ester cholesterol per 100 cc., and the turbidimetric lipids to 43.5 KU. There has been no essential change in the phospholipids.

In the past two years the patient has developed mild angina; his ECG and BCG are still normal. There has been no return of skin lesions. (Table IF.)

Group B (see Table II)

H. S., 47-year-old white male upholsterer, was first seen in 1944 because of painful tumors of both hands of two to three years' duration. The patient was not certain but believed it was around 1940 that he first noted onset of yellowish tender nodules in flexion creases and soft tissue of fingers and hands. The first lesions consisted of yellowish, tender nodules appearing on palms; later similar tumors developed on the elbows, knees, over buttocks and Achilles tendons. Except for the pain due to pressure and unsightliness of the lesions, he had no symptoms. He was treated for several years at the Skin and Cancer Hospital with local medication, Fowler's solution, insulin, x-ray, thyroid substance, and excision of some of the

larger tumors. Nevertheless, new lesions kept appearing.

There was no family history of diabetes mellitus, heart disease, or xanthomatosis.

General physical examination, including ECG and BCG, was within normal limits. The cutaneous lesions consisted of yellowish-red firm tumors embedded in the skin of the palms, particularly of the flexor surfaces of the fingers, many similar tumors in the skin over elbows and knees, and studded over buttocks. The lesions were, in general, discrete but sometimes confluent, and varied from pinhead sized nodules to 1 by 2 cm. tumors and 6 by 7 cm. flat plaques. Besides the cutaneous lesions, fusiform masses attached to tendons could be felt in all extensor tendons of the fingers, both quadriceps and both Achilles tendons. Scars from several previous operative interventions were located over the knees and Achilles tendons, and there were several areas of radiation dermatitis, particularly over the heels.

Laboratory examinations showed a fasting blood sugar of 80 mg. per 100 cc., BMR +12, normal glucose tolerance and urinalysis, negative STS, total serum cholesterol level of 685 mg. with 370 mg. esters per 100 cc., turbidimetric lipids of 87.1 KU, and normal liver function tests. A biopsy was reported as xanthoma tuberosum.

The patient was placed on a 50 Gm. fat diet. Over a six-month period there was no effect on either serum cholesterol levels or skin or tendon lesions. In March 1951 he was placed on the 20 Gm. fat diet. In the next twelve months the serum cholesterol level gradually fell to 441 mg. total and 268 mg. esters per 100 cc. The total lipid fell to 59.8 KU, and the phospholipid from 25.0 to 16.0 mg. P per 100 cc. During this period, even though the patient in general adhered well to diet, there were fluctuations that could be explained by minor changes in fat intake (i.e., an increase of 10 Gm. fat per day in the diet caused a rise in the serum cholesterol level of 200 mg. per 100 cc.). Even though the serum cholesterol level fell considerably, no change was noted in the size and consistency of tendon lesions and there was only minor involution of skin lesions. The ECG and BCG remained normal. (Table IIA.)

L. W., 41-year-old white housewife, was admitted to the Hospital of the University of Pennsylvania ward service in November 1949 because of severe angina pectoris. Since childhood she had had large tumor masses attached to all palpable tendons, somewhat painful on slight trauma, which interfered slightly with joint motions. About 14 of these pendulous tumors had been removed surgically, and others had been irradiated without any significant beneficial effect. Since age 27 the patient had had episodes of substernal pain, radiating to the left arm, neck and mouth, brought on by exertion, eating, exposure to cold, excitement, and lying flat. For at least ten years the patient had been awakened at night by such attacks of pain. Palpitation usually accompanied the pain. Orthopnea and exertion dyspnea were marked. For the past eight to ten years she had had symptoms of cholelithiasis.

There was no family history of diabetes mellitus or xanthomatosis, but her mother had heart disease.

Physical examination on admission showed a moderately well nourished white female, anxious, in distress, complaining of chest pain and quite orthopneic. Except for a soft systolic murmur at the apex and moderate hypertension (190/85), the general physical examination was not remarkable. Along all palpable tendons and over pressure areas were multiple irregular firm masses, obviously attached to and moving with tendons, most marked along the extensor tendons of fingers, biceps, quadriceps, and Achilles tendons. All lesions were subcutaneous and had a yellowish translucent sheen. There were no intracutaneous nodules. Many operative scars were noted, and there were areas of x-ray atrophy over elbows and knees.

The ECG showed marked ST segment depression in nearly all leads, particularly in the medial chest ones. Exercise caused even more marked ST segment depression. The BCG showed marked hypokinemia, subnormal circulation, I-J and J-K notching and abnormal form.

Laboratory examinations showed normal glucose tolerance, a fasting blood sugar of 80 mg., serum cholesterol level of 688 mg. with 396 mg. esters per 100 cc., total turbidimetric lipids of 58.1 KU, phospholipid 15.5 mg. P per 100 cc., and normal liver function tests. X-ray examination revealed cholelithiasis with good gall bladder function and calcification of the abdominal aorta. Tendon biopsy was reported as xanthoma tuberosum.

The patient was placed on the 20 Gm. fat diet in February 1950, but did not adhere well to it until March 1951. During this period of time there was no significant change in serum cholesterol levels, tendon lesions or angina. From March 1951 to November 1951 she adhered well to the restricted diet. Her serum cholesterol level fell to 440 mg. total and 274 mg. ester cholesterol per 100 cc. There was not much change in the total turbidimetric lipids. The phospholipid rose to 23.5 mg. P per 100 cc. There seemed to be considerable symptomatic improvement in patient's angina pectoris, although, due to the marked emotional overlay, accurate estimation of improvement in symptoms was difficult. There was no improvement in the ECG and tendon lesions. The most dramatic changes took place in the BCG. The calculated cardiac output rose markedly, I waves reached below baseline and the configuration of the waves returned to normal. Shortly before the patient's death there was some deterioration in the BCG. On November 11, 1951 after an episode of severe chest pain lasting six hours, the patient suddenly died of acute myocardial infarction as evidenced by ECG taken two hours prior to her death. (Table IIG and Figure 5.)

R. C., 4-year-old male white child was admitted to our clinic in May 1951 because of yellow nodules over the heels and knees. At age two years, his mother noted the development of yellow, pin-point nodules over both Achilles tendons. These grew fairly rapidly over a four-month period, developing into plaques of 6 mm. in diameter. The lesions were destroyed by desiccation by his family physician, only to reappear quite rapidly and continue to grow. Four months prior to admission a third lesion appeared over the right patella. There were no systemic symptoms, and the patient had been developing normally as far as could be determined.

There was no family history of diabetes mellitus or cardiac disease. Both mother and father are obese. The serum cholesterol level of the mother was reported as 396 mg. and that of the father as 412 mg. per 100 cc.

General physical examination on admission was entirely within normal limits for a 4-year-old child. In the skin over both Achilles tendons there were single yellowish-red nodules, 8 mm. in diameter, with slightly depressed center and some superficial telangiectasia. A similar nodule, 3 x 4 mm. in diameter, was located in the skin over the right patella. No tendon lesions were noted.

Laboratory examination showed a fasting blood sugar of 94 mg., total cholesterol level of 1200 mg. with 765 mg. esters per 100 cc., total turbidimetric lipids 156.8 KU, phospholipid 33.9 mg. P per 100 cc. and normal liver function tests. The ECG and BCG were normal.

The child was placed on the 20 Gm. fat diet and apparently has adhered well to it. In the subsequent nine months the serum cholesterol level has fallen to 699 mg. total, with 456 mg. esters per 100 cc., total turbidimetric lipids to 63.4 KU, and phospholipid to 22.3 mg. P per 100 cc.

In spite of the slow but significant fall in serum cholesterol levels, the lesions have increased somewhat in size, and tendon nodules in the extensor tendons of both hands and in the right Achilles tendon have appeared. (Table IIC.)

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Resumen

El empleo terapéutico de regímenes pobres en grasa y en colesterol. I. Tratamiento de la xantomatosis familiar esencial

(1) A nueve pacientes con xantomatosis familiar esencial probada les ha sido administrado un régimen pobre en grasa y en colesterol, y han sido observados durante períodos de tiempo que variaban de 8 meses a 7 años. El régimen estaba ajustado para contener unos 20 g. de grasa total y 100 mg. de colesterol por día.

(2) Todos los pacientes mostraron un descenso notable del nivel de colesterol en el suero mientras que siguieron el régimen. En los pacientes sin lesiones de los tendones, el colesterol sérico volvió a límites normales o casi-normales. En aquellos con xantómata de los tendones la respuesta fué mucho más lenta, menos dramática, e incompleta.

(3) Xantómata cutáneos, a no ser acompañados de tumores de los tendones, involucionaron parcial o enteramente. Una disminución del tamaño de las lesiones comenzó a efectuarse a los 2 o 3 meses después de iniciarse la terapéutica. Ninguna alteración fué observada en los pacientes que tenían lesiones tanto de los tendones como cutáneos. En uno—un niño—lesiones de los tendones aparecieron mientras que seguía el régimen.

(4) Todos los pacientes con angina pectoris mostraron una mejoría clínica.

Una normalización progresiva del trazado balistocardiográfico se observó en dos de los pacientes; en otro el trazado varió concomitantemente con la presencia probable de un pequeño infarto. Reaparición de la pulsación en los vasos antes no palpables de las piernas y disminución de la claudicación intermitente, observadas en dos pacientes, indica una mejoría en la circulación de las arterias periféricas de mediano calibre. Parece, pues, que la adherencia a un régimen pobre en grasa y en colesterol pueda traer una mejoría de los síntomas ateroscleróticos, tal vez por promover la reabsorción de los depósitos ateromatosos.

OVERNUTRITION *and* OBESITY

By H. H. MITCHELL, PH.D.

FORTUNATELY, men do not live under constantly optimal conditions, protected against adverse factors, like experimental rats in an air-conditioned nutrition laboratory. They have their vicissitudes and even occasional physiological crises. Otherwise, life would be dull indeed.

The animal body is flexible in meeting these varying conditions. Even if the food supply should be inadequate, and undernourishment result, the adaptive powers of the human body will enable it to adjust to the situation.[1] For, as accumulating evidence indicates, the nutrient requirements of man and animals are not fixed quantities.[2]

It is hardly conceivable, however, that the voluntary food consumption of men will exactly compensate for the demands brought on by these crises. It is a wise procedure, therefore, to include in the food supply amounts of the essential nutrients in excess of day-to-day requirements. Dietary standards and recommended allowances are constructed on this premise.

These excess supplies of essential nutrients are stored in the tissues and are available to supplement temporary deficiencies in the diet. The maintenance of these stores at the desired levels may in many cases call for continuous high levels of intake. "Overnutrition" is thus good nutrition, because it is insurance against the necessity of raiding essential tissues of the body to provide energy and nutrients for its proper functioning when the food supply fails to do so. It is also the usual type of nutrition in human populations where food supply and economic conditions are favorable.

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"VITAL" AND "REDUCIBLE" TISSUE COMPONENTS

Attempts to divide the tissues of the body into an "active protoplasmic mass" and an inactive non-protoplasmic mass have resulted in failure, because of the absence of any sharp distinction between living tissues on this basis. All tissues are active in the sense that they respire and consume oxygen, with the exception of the outer protective covering of the body, the integument and the integumental structures, representing keratinized tissue, and probably the albuminoid matrices of bone, teeth, and cartilage. The dynamic state of the body tissues, including the adipose tissues and the bones, has been revealed by Schoenheimer and his associates[3] and by many others.

However, it is possible and important to an understanding of the processes of growth and of nutrition to divide the body tissues into a part that is necessary for the life of the organism as a whole, and a part that is dispensable, and can be sacrificed to maintain life under adverse conditions. Nash[4] has distinguished these segments of the body as the "vital portion," necessary for continued existence, and the "reducible portion" that may be sacrificed. The former segment "... does not include all of the normal complement of living protoplasm of the organism, since loss of protoplasm occurs during extended periods of inanition without loss of life." The reducible portion includes living protoplasmic material, but not the keratinized tissues or the albuminoid matrices above referred to, which are entirely or very largely[5] beyond the reach of catabolism and hence not reducible.

All of the nutrients are involved in the formation and the maintenance of the "vital" and the "reducible" segments of the animal body.

Overnutrition, obviously, is related to the reducible segment of the tissue nutrients, and the problems of overnutrition concern the weighing of any benefits resulting from the accretion of reducible nutrients against the hazards if any, involved in their excessive accumulation in the tissues.

Reducible Tissue Proteins. Whipple and his associates early distinguished between what they called "dispensable" and "indispensable" tissue proteins. This work has been well summarized recently by Whipple.[6] The blood plasma proteins, especially the albumins, and the liver proteins are preëminent as dispensable (or reducible) proteins, which, either because of chemical peculiarities or of a more exposed location in the cell with reference to proteolytic enzymes, are more readily drawn upon as a reserve material than other proteins more intimately involved in protoplasmic functions. The role of the liver as a storage depot for dispensable protein has been presented by Kosterlitz and Campbell.[7] The nature of dispensable liver proteins is revealed either by feeding experimental animals high-protein diets and noting the change in liver composition, or depleting the animals by specific protein inanition and noting the nature of the resulting catabolites. From such studies Kosterlitz[8] has concluded that "protein and phospholipin were lost or gained at practically identical rates, while the changes in nucleic acid were of smaller magnitude." Allison[9] also has shown that the cytoplasmic proteins of the liver are decreased most rapidly in specific protein inanition, and that the higher the protein reserves built up by prior high protein feeding, the greater the resistance to severe protein depletion, however imposed.

Dispensable tissue protein, sometimes called "deposit protein," is stored in the body only when the protein intake is raised above current needs for indispensable protein in growth or replacement of endogenous losses, or when a prevailing high level of protein feeding is spared by supplements of dietary carbohydrates or fats. They are depleted when the protein intake is lowered, or when emergency demands for protein occur, as in hemoglobin or plasma protein regeneration, or when protein catabolism is increased by inflammation, bone fracture,[10] superficial thermal burns,[11] hyperthyroidism, surgical trauma, and probably many other contingencies. These protein stores contribute nothing, as far as is known, to the normal functioning of protoplasm, but they may exert a protective function when the body is subjected to the strain of anesthesia (particularly chloroform poisoning), arsphenamine, and the like. Whipple has well characterized these stores as a bulwark against infection and other types of tissue damage. The advantages of generous pre-operative protein feeding seem obvious, since the large negative nitrogen balances, which are characteristic of severe surgical operative loads and represent a considerable depletion of protein stores, are so resistant to protein feeding.[12]

The disadvantages of protein overnutrition have in the past been greatly exaggerated, and may not exist at all in practical human nutrition; even in nephritis, it seems to be more important to replace by high protein feeding the protein lost in the urine than it is to spare the kidney the work involved in excreting protein metabolites.[13] Certainly the high protein feeding of healthy young adults, 305 Gm. of protein daily for 5.5 months, did not occasion any symptoms of metabolic disturbance,[14] or of kidney damage.

The accumulation of protein stores from dietary sources is accomplished in an increasingly wasteful manner as the plane of protein nutrition increases, apparently because the higher the percentage of protein in the diet the greater the proportion that is diverted from anabolic reactions to the oxidative reactions which yield energy to the tissues, including the specific dynamic action of the food.[15]

Reducible Mineral Stores. The skeleton contains enormous stores of calcium salts, accounting for over 99 per cent of the total body calcium. Furthermore, the animal body contains a specific calcium mobilizing agent in parathormone. Hence, calcium deficiency in an animal is very difficult to impose, even over a long period of negative calcium balance. The fact that deficiency symptoms eventually develop long before the skeleton is depleted of

calcium,[16] even though vitamin D is supplied in generous amounts, implies that skeletal calcium may be divided into a readily reducible portion and into a portion which is immobile for all practical purposes. Bauer, Aub, and Albright[17] seem to have been the first to demonstrate in experiments on kittens that the bone trabeculae contain the most mobile calcium. As the authors remark:

"This raised the question, are the trabeculae a reserve supply of calcium? Is it possible that the calcium in the bones can be divided into two parts—a large portion making up the structural part of the bone, which functions as a mechanism for body support, and a smaller, less stable, portion acting as a reserve depot, for use when the body needs calcium or inorganic salts? The anatomical structure of the trabeculae is in accord with such a theory. They are most numerous at the epiphyseal ends of the bones, where the blood supply is greatest. These delicate, lacelike structures, in close relation to the bone marrow, are well situated to receive calcium deposits in times of calcium excess, and to give up calcium in times of calcium demand."

Bone trabeculae are depleted during subsistence on an inadequate calcium supply, during rapid growth or long-continued administration of parathormone. On the other hand, the administration of a high calcium diet to calcium-depleted cats leads to an increase in the number of trabeculae,[18] especially if irradiated ergosterol is given concurrently. This conception of two forms of calcium stores in the bones has been well confirmed by experiments on rats with the use of radio-calcium.[19]

The situation with reference to phosphorus is somewhat different. Although also present in the bones in large amounts its mobilization is more difficult, probably because of the lack of specific mobilizing agents. As a result, the mobile stores of phosphorus, wherever they may be, are soon exhausted and the symptoms of aphosphorosis develop soon after an animal is placed upon a diet severely deficient in this element.

The stores of other minerals in the body are probably divisible into vital and reducible fractions, since animals lose essential minerals by excretion for variable periods of time after receiving diets deficient in such minerals. A "labile pool" of iron has been inferred by Greenberg and Wintrobe[20] from the results of experiments on the injection of radioactive iron into rats.

Overnutrition with reference to minerals is advantageous in keeping labile stores replenished to a reasonable extent in order to meet temporary emergencies, or situations such as pregnancy involving sharply increased demands for minerals. Such overnutrition probably exists in most communities in this country where local crops are not abnormally low in minerals because of soil depletion. In the latter cases[21] special dietary measures should be taken to meet the peculiar conditions prevailing. The harmful effects of mineral overnutrition relate not so much to the accretion of excessive reducible stores in the tissues, but rather to the toxic action of even small concentrations of such essential elements as copper, cobalt, manganese, and zinc in the diet. According to Kinney, Hegsted, and Finch,[22] excessive absorption of iron by adult rats may lead to excessive hemosiderosis of the hepatic parenchyma and of the reticuloendothelial system. The iron content of the liver was found to be greatly increased. This evidence of the absorption of iron far beyond current needs for iron is incompatible with the theory current in many quarters in this country to the effect that the absorption of iron is regulated by the need of the body for iron, a theory that is insecurely based upon valid evidence, and one that requires an unrestrained imagination for acceptance.

Reducible Vitamin Stores. The tissues are able to store vitamins in proportion to the amount in the food supply. When the food supply of vitamins is so low as to induce eventually pathological symptoms of deficiency, the tissues still contain appreciable amounts. In unpublished work by Pfander from the author's laboratory it was shown that in the guinea pig a reduction of the ascorbic acid concentration of the adrenal glands by subsistence on a diet low in the vitamin to a value of about 63 μg per cent was associated with incipient signs of ascorbic acid deficiency, i.e., hypertrophy of the adrenal glands and impairment in the growth of the odontoblast cells in the incisor teeth. This level of ascorbic

acid storage in the glands which concentrate ascorbic acid to the greatest extent, corresponds to the vital stores of the vitamin. Anything above this level brought about by overnutrition with reference to ascorbic acid would constitute reducible stores.

Schultz and others[23] measured the storage capacity of rat tissues for thiamine (vitamin B_1) storage. The thiamine content of the body increased as the dietary intake was raised from 15 to 65 μg daily, until a maximum concentration of 2 μg per Gm. of body weight was attained. The same relation between intake and storage was observed by a group of Wisconsin investigators[24] in experiments on rats with thiamine, riboflavin, and nicotinic acid. At Cornell University[25] the building up of reducible stores of ascorbic acid in adult human subjects has been observed and measured.

Hickman[26] has proposed a hypothesis that the rate of depletion of the body's (reducible) reserves of a vitamin is directly proportional to the reserves present in the body at the time. A beautiful confirmation of this theory as it relates to reducible stores of vitamin A was supplied by Frey and Jensen.[27] These authors measured the liver stores of vitamin A in 120 Hereford steers taken from pasture, placed on a fattening ration consistent with good feeding practice, and slaughtered at periods ranging from 0 to 166 days on the latter low-carotene ration. The logarithm of the concentration of vitamin A in the liver varied linearly with time on the depletion diet, in such a manner that the half-life of the original vitamin store (51.4 μg of vitamin A per Gm. of liver) was 35.07 days.

In practical nutrition with natural foods, harmful effects of overnutrition with respect to the vitamins have never been reported to the knowledge of the author. Experimentally, or in vitamin therapy, pharmacological effects may be produced with vitamin A, vitamin D, nicotinic acid, and probably with other vitamins. Undoubtedly there are favorable effects of a certain magnitude of reducible vitamin stores as insurance against unanticipated demands for these nutrients. The recommended allowances for the vitamins proposed by the Food and Nutrition Board of the National Research Council[28] probably contain sufficient over-supplies above current needs to provide enough reducible stores for this purpose.

Vital and Reducible Energy Stores

Glycogen and fat are *per se* the energy storage components of the tissue. There seems to be an irreducible minimum of both compounds in the animal body. Drastic means indeed must be employed to reduce either to the vanishing point without destroying life itself. Wertheimer and Ben-Tor[29] studied the amount of glycogen in the tissues of rats subjected to different degrees of undernutrition. After the last meal, these undernourished animals, as compared with well-nourished controls, showed an intensive synthesis of glycogen in the different adipose tissues of the body. With an inadequate energy supply they still were under the necessity of providing a minimum amount of glycogen to their tissues.

Newly born mammals contain minimal amounts of fat, generally amounting to 2.5 per cent or less, though the human infant at birth has been found to contain 16 per cent of fat.[30] As extra-uterine growth proceeds, the percentage of fat in the body increases at a faster rate in the female than in the male. But whenever growth occurs fat is deposited, even when the rate of growth is greatly retarded by a restricted food supply. It seems evident that there is a vital storage of fat as well as of glycogen in animal tissues. Nash[4] concludes from his experiments on 3-month-old rats fasted until death that, of the original fat content, 5 per cent remained after death ensued, being evidently a portion, at least, of the vital store of fat.

During normal nutrition both the glycogen and the fat stores exceed the limits of the vital stores,* as do other nutrients. The capacity

* It may be noted here that this condition could not be assured if the recommendations of the National Research Council[28] for adult men and women are followed. For a 70 Kg. man doing sedentary work, 2400 cals. per day are recommended, equivalent to an energy expenditure, exclusive of the S.D.A. (Specific Dynamic Action), of 2160 cals. Assuming an average height of 5 ft. 8 in. (174 cm.), the basal metabolism at 21 years of age would be 1758 cals.

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for storing glycogen is known to be limited, equaling about 500 to 700 Gm. in adult man. On the other hand the capacity for fat storage is enormously greater. In farm animals fattened for the market, fat contents of 50 or 60 per cent of the entire carcass have been recorded.[31] Although in the human, recorded analyses of cadavers have not shown more than 24 per cent of fat, indirect estimates from appropriate measurements of the living body have indicated values as high as 44 per cent for obese men (190 per cent of "ideal" weight) and 58 per cent for obese women (230 per cent of "ideal" weight).[32]

The proportion of maximal reducible stores of fat to vital stores of fat greatly exceeds that of any other nutrient, organic or inorganic. Beyond a moderate concentration of 15 to 20 per cent, accumulations of fat in the body would seem to serve no useful physiological purpose. The supposed deleterious consequences of such fat accumulations have been widely publicized.

Obesity: Its Inception

The term "obesity" defies precise definition. The term is a useful one, connoting a condition of the body in which fat accumulation is so great as to impair physiological efficiency and well-being. In all cases, regardless of its primary cause, it is due to the consumption of food energy beyond current needs, either for some period in the past if the condition is static, or in the present, if the condition is progressing. This hyperphagia may be produced experimentally by the administration of an appetite stimulant such as insulin, or by a hypothalamic lesion, involving the neurons lying on or in the region of the ventromedial nuclei, or by the ingestion of thyroid depressant drugs, such as thiouracil (or one of its derivatives), or by a hormone-active drug, like diethylstilbestrol. Naturally, it may result from a restriction of activity following an active life, an effect that would be augmented by an especially appetizing diet. If the experience obtained with laboratory animals[33] may be applied to man, an unbalanced diet, too low in protein for example, would be expected to favor fattening rather than normal growth in a child.

The dominance of hereditary factors in human obesity is emphasized by Davenport,[34] Gurney,[35] and Angel,[36] and in animal husbandry in the production of fat pork carcasses by Dickerson.[37] The association of familial constitutional types with obesity and its opposite is a common observation. According to Angel:

> "Inheritance of potentialities for obesity involves several gene complexes, probably including a sex-linked recessive semi-lethal as well as dominant factors. These probably influence both hypothalamic sensitivity (controlling appetite) and body build, through effects on the ending and speed of growth."

According to Gurney: "A study of the progeny of different parents indicates segregation, which is evidence of mendelian inheritance of build." A premise in constitutional anthropology is that the components of an individual's somatotype (see Sheldon et al.[38]) remain constant after skeletal growth is completed. A significant inverse correlation has been shown to exist between the endomorphic component

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(Harris-Benedict standard), representing an "activity increment for effective living" of only 402 cals., equivalent to 23 per cent of the basal metabolism. For a woman weighing 56 Kg., the recommendation is 200 cals., or 1800 cals. exclusive of S.D.A., which is again taken at 10 per cent of the total fuel value.[15] Assuming a height of 5 ft. 4 in. (163 cm.), the basal metabolism of the woman by the same standard, at age 21, is 1394 cals. per day. The recommended allowance exclusive of S.D.A. is 29 per cent above the basal expenditure.

The "energy increment for effective living"[53] is commonly assumed to be 50 to 60 per cent, rather than 23 to 29 per cent, of the basal metabolism. According to data cited by Carpenter,[54] the energy cost merely of sitting quietly is 38 per cent of the basal expenditures of a man of the above description. Experiments on college women carried out at the University of Illinois[55,56] indicate that such subjects, carrying on their ordinary duties as students, require an energy increment of 80 to 90 per cent over their determined basal expenditures to maintain body weight, for a period of 105 days in the latter experiment. These subjects were on continuous dietary control.

The energy requirement estimated by Orr and Leitch[57] for a clerk, equivalent to an activity increment of 54 per cent of the basal energy expenditures, is much more realistic than are those of the N.R.C.

of body build and the specific gravity of the body,[39] which in turn is highly and inversely correlated with overweight and adiposity.[40]

"Variations in build," according to Davenport, "are not to be accounted for merely by variations in intake and outgo of calories, but also by the endogenous factors that determine the 'economy of nutrition' or the cost in energy of adding an additional kilogram of weight to the body. The factors involved in producing differences in these respects are hereditary factors."

An immense amount of research has been devoted to the metabolism of obesity, in an attempt to explain its inception on physiological grounds. Obesity, uncomplicated by endocrine dystrophy, has not been shown definitely to be associated with a lowered basal metabolism, with a lowered specific dynamic action of the food, or with a greater efficiency in the digestion of food.

To the author it seems probable that each somatotype in constitutional build is associated with a "homeostatic" mechanism, borrowing a term and concept from Cannon, which is concerned in the maintenance of a stable body weight and a stable content of reducible fat stores. The mechanism must involve both appetite control mediated through the hypothalamic feeding center, and the conversion into heat of food consumed above current needs, the specific dynamic action. In different somatotypes the efficiency of the homeostatic mechanism varies. It is most efficient in ectomorphy, the slender and wiry type. Certainly it is least efficient in endomorphy, the soft, round type. In endomorphy, when homeostasis is aided by voluntary control of food consumption, overweight can be avoided or kept within bounds. Such overweight as develops is maintained in a static condition only by conscious and intelligent control of the diet. Injudicious food habits will, in this type of individual, break down the homeostatic mechanism and progressive obesity will ensue. Probably, as Angel believes, the breakdown of homeostasis in this type of individual is accelerated by social stress and frustration, based upon psychological instability characteristic of endomorphy. The ectomorphic individual maintains his body weight without conscious effort or deliberate dietary control.[41]

The failure of physiologists to explain body weight homeostasis, the existence of which in certain somatotypes is common knowledge, is probably due, first, to the slow progress in elucidating the physiological factors that determine appetite and particularly the feeling of satiety, and, second, to the experimental difficulty in measuring completely the total extra calories produced above the basal metabolism after a meal, the S.D.A. Human subjects will rarely remain quiescent for the time necessary (10 to 12 hours or more) to dissipate this food energy waste. The difference between endomorphy and ectomorphy in the disposition of food energy may rest not so much in the peak specific dynamic effect as in its duration. Also, the most crucial experiments of this kind, if a distinction between somatotypes were under study, would relate to the calorigenic effects of large meals, not of moderate or small ones so commonly used in such studies.

The inevitability of the conclusions expressed above is well stated by Hagedorn, Holten, and Johansen[42] in the following words:

> "It is certain that a regulation of the body weight takes place. When we consider that minimal amounts of fat must be stored per day in order to produce a considerable increase in weight and compare them with the daily intake of food, it is easily seen that this regulation must be delicate, so that it seems improbable that the appetite should be the only regulating factor. This is evident from the fact that many persons are induced by habit and external conditions to take amounts of food which cannot possibly depend exclusively on their appetite. The problem, therefore, cannot be put as a simple addition and subtraction of the intake and expenditure of the organism."

This thesis led them to the working hypothesis "that obesity in many cases might be due to an abnormally increased transformation of carbohydrate into fat." Their study of respiratory quotients of normal and obese subjects in the post-absorptive period after a standard meal offer circumstantial support to this hypothesis, which would also involve differences in S.D.A., since dietary carbohydrate transformed into fat could not contribute to the oxidative metabolism.

Obesity: Its Relation to Disease

An excellent discussion of the relation of obesity to health and disease has recently been published by Armstrong and others[43] based upon the morbidity and mortality records of the Metropolitan Life Insurance Co. Defining overweight as "any deviation of 10 per cent or more above the ideal weight for the person," they demonstrate, as has been done many times before, an association between overweight and the incidence of hypertension, significant deviations from normal electrocardiograms, atherosclerosis, diabetes, gall bladder disease with clinical symptoms, cancer of the genital organs in women, degenerative arthritis, kidney function impairment, and shortened life span.

Not only do the authors give to these statistical associations a direct causal interpretation, but also—by implication, at least—they designate obesity as the cause and the disease as the effect, as is obviously apparent from the following quotation from their discussion:

> "Obesity, lying in the twilight zone between health and disease, is a logical point of assault on the medical problems of older persons. Weight control is a positive approach to the maintenance of health and prevention of some of the major diseases of middle and later life."

The author is not competent to pass upon the medical questions involved in this argument. He wishes merely to point out that to the extent that the evidence for the implication of obesity in the *causation* of the many diseases listed above rests upon a greater incidence of these diseases among the obese than among persons of normal weight, it is open to serious question. The demonstration of a correlation of two variables may be causal in nature, or it may be a result of a common cause for both. If the correlation is directly causal in nature, it has still to be determined which variable is the cause and which the effect. Logically, to interpret the association of obesity with hypertension as meaning that hypertension can be cured by removing the obesity, is no more convincing than to interpret the association of cachexia with cancer as meaning that cachexia causes cancer and that the nutritional rehabilitation of the patient will cure the cancer.

It seems a bizarre idea that obesity should be the "cause," direct or contributing, to so many diseases affecting so many different tissues. The facts known about the physiology of adipose tissue[44] do not lend support to the idea. It may be noted also that these diseases of later life occur not infrequently in lean individuals.

The question is not of academic significance only, because if the simultaneous occurrence of obesity with cardiovascular disorders, diabetes, gall bladder disease, certain types of cancer and arthritis, kidney impairment, etc., depends upon a common cause for disease and overweight, such as an associated diathesis traceable to the germ plasm, then the cure or alleviation of the disease by weight reduction is problematical.

Armstrong and associates apparently were troubled by the same disturbing thoughts, for they write:[43]

> "In spite of the evidence that has accumulated on the serious effects of overweight on health and longevity, and the wise dissemination of this knowledge to both physicians and the general public, there is surprisingly little information available on the long-term results of weight reduction, either as a hygienic measure for prevention of disease or as a procedure in the treatment or alleviation of various diseases and conditions. Adequate long-term studies of weight reduction are few and indicate that only a minority of overweight persons persist in their effort to reduce long enough to reap the greatest potential benefit. Beyond that, we lack properly controlled studies to show whether or not the benefits of weight reduction in terms of health and logevity are as real and substantial as they are assumed to be. A real need exists for new and better data on many aspects of weight reduction."

The only report of the kind that they consider worthy of citation is a report by Newburgh[45] to the effect that in 77 per cent of 47 adult obese patients the lowered sugar tolerance often associated with obesity was corrected by weight reduction. Newburgh does not consider these patients diabetic in the usual sense, nor does he consider that obesity aggravates an "inherent pancreatic weakness."

Obesity: Its Remission and Avoidance

The undesirability of overweight from the standpoint of comfort and health is so obvious, even though much of the evidence for a causal relationship of obesity to specific diseases is incomplete, as to render reduction of weight in the obese desirable. The abdominal ptosis and consequent postural imbalance that, according to Kerr and Lagen,[46] develop in obesity and help to produce the dyspnea, cardiac embarrassment, dizziness and headache, shortened stature, and poor "energy economy" in itself is justification for the removal of excessive fat stores.

Increase in energy expenditures is a procedure of doubtful value in weight reduction, first, because the energy cost of fairly considerable muscular feats is so small,[47] and, secondly, because muscular exercise is a potent stimulant to appetite.

Dietary restriction is the most effective plan for weight reduction and for the avoidance of obesity in those persons who are hereditarily, or for other reasons, susceptible to this condition. The advice of Barborka[48] on this matter is sound and concise:

"The important factors in prescribing quantitative reduction diets are secured by applying the following principles: the diet must be (1) low in calories, (2) relatively high in protein, (3) moderately low in carbohydrates, (4) very low in fat, (5) sufficient in bulk to satisfy hunger, and (6) adequate in vitamins and minerals."

The importance of limiting severely the consumption of fat cannot be overemphasized. Fat, of all organic nutrients, possesses the greatest caloric density, two and a quarter times that of carbohydrate or protein. Of all organic nutrients, dietary fat is most readily converted into adipose tissue fat. If the S.D.A. of each organic nutrient is expressed as a percentage of the fuel value contained in the test portion, the evidence is overwhelming for human subjects and for the lower animals[49] that the S.D.A. of fat is less than that of carbohydrates, "meaning that less of the energy of fat is lost as animal heat and therefore more is available for deposition." Judging from experiments on the laboratory rat, the inclusion of fat in a diet depresses the specific dynamic action of nutrient combinations in a diet more than does glucose or protein.

From the analysis of the non-protein respiratory quotient, (R.Q.), Forbech[50] concludes that in obesity in man, in which quotients exceeding 1 are seldom if ever observed, the fattening process results only, or predominantly, from the direct transfer of dietary fat, with little metabolic modification, into depot fat, a process that does not modify the prevailing R.Q. Only in animals that have been developed by selective breeding over many generations for fat production, such as the lard type of pig, has the ability to form fat from carbohydrate been enormously accentuated.[52]

In this connection, it may be noted that hereditarily obese mice, when offered a choice of 3 diets consisting essentially of pure fat, carbohydrate, or protein, fortified with vitamins and minerals, selected the fatty diet predominantly. An average of 52.2 $\pm$ 6.6 per cent of the total calories consumed was provided by fat, as compared with 28.8 $\pm$ 8.4 per cent for non-obese mice.[51]

Conclusions

The storage of all essential nutrients in the body may be "vital" or "reducible" in character depending upon the essentiality of such stores to the continuance of life. The "reducible" stores are the result of overnutrition in the sense that at the time, or during some previous time, an excess of the respective nutrients over current requirements is being, or has been, consumed. The reducible stores are not known to be involved in the life processes until they are mobilized to meet demands for nutriment beyond the capacity of the current food supply, or sudden unavoidable demands in emergencies. These reducible supplies in moderate amounts are useful insurance and, under favorable nutritional conditions, are provided by the food. Their benefits to human welfare warrant moderate overnutrition, and moderate overnutrition with proteins, minerals, and vitamins rarely indeed presents any hazard to health.

Stores of fat resemble stores of other nutrients in that they may reasonably be separated into "vital" and "reducible" portions, but unlike the other nutrients, the reducible portion can be increased to such an extent as to impair wellbeing and health, and probably to shorten the normal life span. Hereditary factors, determining the somatotype of the individual, seem to dominate the inception of obesity. Endomorphy in particular involves apparently an inefficient homeostatic mechanism for the maintenance of body weight, permitting a complete breakdown of homeostasis if dietary habits are not kept under constant surveillance. Other factors are, of course, involved.

The evidence for the involvement of obesity in the etiology of a variety of diseases affecting later life and many organ systems seems to be incomplete in so far as a direct causal relation of obesity to disease is assumed, on the basis merely of a greater incidence of these diseases among obese than among non-obese persons. Whether weight reduction is effective in avoiding these degenerative diseases, or in curing or alleviating them when present, is problematical. The disadvantages of excessive overweight, however, cannot be doubted, and the greater effectiveness of dietary restriction is evident. Emphasis should be placed on restricted consumption of fatty foods in particular, for many reasons discussed in the text.

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Resumen

El almacenaje en el cuerpo de todos los principios alimenticios esenciales puede ser de carácter "vital" o "reducible," dependiente de la esencialidad de tales reservas al mantenimiento de la vida. Las reservas "reducibles" son la consecuencia de la hipernutrición, en el sentido de que actual o previamente un exceso de los respectivos principios alimenticios sobre las necisidades basales está siendo o ha sido consumido. A las reservas reducibles no se les reconoce el papel que desempeñan en el proceso vital hasta que se mobilicen, sea en respuesta a demandas nutritivas en exceso de la capacidad de la alimentación corriente, o bien para afrontar a las demandas súbitas e inevitables en las crisis. En cantidades moderadas, estas reservas reducibles sirven de "seguros," y en estados de nutrición favorables, son proporcionadas por los alimentos. Su contribución al bienestar humano justifica una hipernutrición moderada—y al ser esta de proteínas, minerales y vitaminas, muy raramente presentará algún peligro para la salud.

Los depósitos de grasa asemejan a los de otros principios, en que lógicamente pueden separarse en porciones "vital" y "reducible," pero a diferencia de los demás, la porción reducible se puede aumentar a tal punto que llegue hasta a perjudicar al bienestar, y con probabilidad, a la duración de la vida. Factores hereditarios, determinantes del somatotipo del individuo, parecen dominar a la incepción de la obesidad. La endomorfia, en particular, está relacionada—según parece—con un mecanismo homeostático ineficaz para el mantenimiento del peso corporal, ineficacia que permite una desagregación completa de la homeostasis, si no se vigila constantemente la dietética. Otros factores, naturalmente, están presentes.

La evidencia para culpar a la obesidad como factor etiológico de una variedad de enfermedades que afectan la postrimería de la vida y muchos sistemas orgánicos, parece ser incompleta, en cuanto pueda asumirse una relación causal directa entre obesidad y enfermedad, basada sólo en la mayor incidencia de estas enfermedades en los obesos que en las personas no obesas. Queda problemático si la reducción del peso sea efectiva en evitar estas enfermedades degenerativas, o bien en curar o aliviarlas, si están presentes. Son indudables, sin embargo, los inconvenientes del peso excesivo, y la eficacia de la restricción dietética es evidente. Hay que poner el énfasis en la ingestión restringida de los alimentos grasos en particular, por muchas razones discutidas en el texto.

Abstracts of Current Literature

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CHOLESTEROL, DIET, AND LIPOTROPIC AGENTS

The current attention to the role of cholesterol in arteriosclerosis has revived interest in the biophysical and physiological aspects of lipid metabolism. Some recent reports which have important practical or potential clinical applications will be described here. The following papers discuss, from different viewpoints, the use of diet and lipotropic agents in arteriosclerosis.

Diet and Lipotropic Agents in Arteriosclerosis. Jack D. Davidson. *Amer. J. Med.* 11: 736, 1951.

This article is one of a group of seminars on arteriosclerosis published in the *American Journal of Medicine*. It summarizes and reviews in a critical fashion the evidence for and against the use of low cholesterol diets and various lipotropic compounds in experimental and human arteriosclerosis. Though it is a review there is considerable unpublished data in this article. There is an extensive bibliography.

The amount of endogenous cholesterol is 10 to 15 times as large as exogenous (dietary) cholesterol and can be formed very readily from many simple compounds such as acetate. Fat supplies these simple compounds most readily and therefore fat as well as cholesterol must be reduced to the vanishing point if any appreciable change in serum cholesterol is to be attained. There is little direct evidence from animal experiments that such diets reduce arteriosclerosis, since this lesion is usually induced in the test animal with high fat, high cholesterol diets with or without thiouracil or stilbesterol depending on the species studied. When normal diets are fed, the lesions regress spontaneously.

Clinical studies which profess to show a greater incidence of arteriosclerosis in obese persons in comparison with lean or semi-starved individuals are open to criticism because the groups compared differ so greatly in age distribution, heredity, and other uncontrolled nutritional factors.

Lipoproteins of the S_f 12–20 type determined in the ultra-centrifuge, which are said to have a positive correlation with increasing arteriosclerosis and coronary artery occlusion, allegedly fall when fat and cholesterol are reduced in the diet. However, the degree of cooperation in taking the prescribed diet was determined by the S_f 12–20 values rather than by dietary control and the correlations noted above have not been confirmed in other laboratories as yet.

There is little evidence favoring the use of choline, betaine, inositol, methionine, and lecithin for the prevention or cure of experimental and human arteriosclerosis even though these agents have "lipotropic" functions and they can provide essential components for phospholipid synthesis. A high level of the latter compounds in comparison with cholesterol seems to be correlated with a low incidence of arteriosclerosis.

The authors point out the pitfalls of animal experiments, particularly investigations on rabbits in this field, and the reasons why so many reported experiments are invalid. In order for an experiment to have significance, there should be at least twenty rabbits in each group, controls should be run concurrently with the experimental animals; sex, age, and weight gain must be the same in each group and frequent serum cholesterol levels must be determined and degree of weight gain observed. When one evaluates experiments in the light of these requirements, there is no indication that choline, inositol,

or lecithin prevent or cure experimental arteriosclerosis though in chickens, choline, methionine, or inositol may reduce the cholesterol level in blood and arterial wall.

In human experiments with these agents, spontaneous fluctuations of serum cholesterol are so great and adequate control regarding development of arteriosclerosis so difficult to attain that no conclusions can be reached.

The author concluded that despite a few individual positive reports, there is no general agreement that choline or inositol have any specific influence upon arteriosclerosis or upon the serum cholesterol level in man or in the experimental animal. As has been emphasized repeatedly, there can be no doubt that obesity, the result of dietary excesses, is commonly associated with advanced arteriosclerosis and premature death but the direct relationship of *dietary* cholesterol and fat to human arteriosclerosis has yet to be proved.—R. W. VILTER

Diet and Lipotropic Agents in Arteriosclerosis. John W. Gofman. *Bull. New York Acad. Med.* 28: 279, 1952.

This article is based on one of the Graduate Fortnight lectures at the New York Academy and reviews the work of Dr. Gofman and his associates up to that point (October 1951). It would appear that of major importance is a new concept of lipoprotein transport of ingested fat. Starting with large lipoprotein molecules, (S_f 40–40,000) the lipid material or lipoprotein is carried through progressively smaller aggregates until it disappears from the blood stream. He also attempts to classify a metabolic defect by the number of these larger aggregates present in the blood.

He has selected the band of S_f 12–100 lipoprotein as an "atherogenic class of lipoprotein" and he reports that the blood level of this band of lipoprotein falls during periods of weight loss. In other patients, the level of this band of lipoproteins drops even when there is no appreciable weight alteration on a diet restricted in total fat intake. These studies may indicate an effect on the dietary fat separate from the caloric weight effect. The human population appears quite "inhomogeneous" in response to fat restriction. An individual's response to a lowering of fat intake is determined by actual trial with serial lipoprotein studies. He further reports the interesting observation that heparin, administered to man, produces a shift in the lipoprotein pattern toward the normal.

This work is at present so controversial that it is only fair to state that many workers in the field disagree with Dr. Gofman and his group. It is also the reviewer's opinion that Dr. Gofman and his group have not satisfactorily answered the criticisms of Dr. Ancel Keys and his co-workers regarding the usefulness of the various lipoprotein bands in predicting arteriosclerosis. Certainly all would agree with Dr. Gofman that weight reduction in the obese is important whether the patient has arteriosclerosis or not. There are many, including the reviewer, who would not agree on the widespread adoption of low fat diets or the necessity for serial lipoprotein studies until there is considerably more evidence of their beneficial effect then we have at present.—C. F. WILKINSON

Lipoproteins in General and Cerebral Arteriosclerosis. A. Simon, J. W. Gofman, N. Malamud, H. B. Jones, F. T. Lindgren. *Am. J. Psychiat.* 108: 663, 1952.

Serum lipoprotein levels (S_f 10–20 class) of a group of patients diagnosed as psychosis with cerebral arteriosclerosis were measured, and found to be similar to those of a group of "normals."

The autopsy findings in 24 cases of psychosis with cerebral arteriosclerosis were analyzed. In 21 cases where the brain was examined, only five showed changes that could be attributed to arteriosclerosis with gross cerebral infarcts. The remaining 16 cases presented a variety of different types of cerebral lesions.—I. A. MIRSKY

Clinical Studies of Blood Lipid Metabolism: II. Blood Serum Variations of Cholesterol, Phospholipids, Neutral Fats, Total Lipids, and Blood Lipid Fraction Percentages in Peptic Ulcer Patients. A. A. Goldbloom. *Gastroenterology* 20: 79, 1952.

The sera of 15 "peptic ulcer" patients were examined for lipid content and the results compared with similar determinations in 15 normal subjects. The arithmetic mean for each of the serum lipid partitions did not differ significantly in the ulcer patients and the normal subjects, but the range of variation in the several values was greater in the patients with peptic ulcer. The failure to demonstrate significant alterations in serum lipids in these ulcer patients was considered significant, since they apparently had been on a high fat and cholesterol diet as part of the treatment for their ulcer disease.—J. E. BERK

Lipids and Proteins of Plasma in Patients with Diseases of the Nervous System. A. A. Fisk, A. Chanutin, and W. O. Klingman. *Arch. Neurol. & Psychiat.* 67: 332, 1952.

The plasma lipids and proteins of patients with a variety of neurologic conditions and psychotic disturbances were determined. No significant difference in cholesterol and phospholipid concentrations of the plasma were found for the control, neurologic, and psychotic groups. Sphingomyelin concentrations appeared to be elevated in patients with neurologic diseases.

A decrease in the albumin concentration of the plasma was noted in both the neurologic and psychotic groups. The authors suggest that the changes noted were not due to the nutritional state since subjects on a semi-starvation diet maintain a normal blood albumin concentration.—I. A. MIRSKY

Lipotropic Agents and Experimental Arteriosclerosis. P. Balatre and J.-F. Merlen. *Gazette méd. de France* 59: 393, 1952.

To study the effects of various lipotropic agents in experimental arteriosclerosis, groups of paired male rabbits were fed a standard diet to which was added a daily dose of 0.50 Gm. of pure cholesterol in 12 cc. of peanut oil. After 45 days, the rabbits were sacrificed. All the control animals showed the histologic lesions of arteriosclerosis and steatosis of the liver. In the animals which had received various lipotropic agents in an attempt to prevent lipoid infiltration, only partial protection was observed. The effects were most marked in the liver. This confirmed earlier experiments, in which it was demonstrated that lipotropic agents act primarily on deposits of fat in the liver, but not on vascular deposits. This is true whether the arteriosclerosis is produced by repeated injections of epinephrine or, as here, by a high cholesterol diet.

Similar experiments were conducted on Leghorn chickens, grouped in 7 lots of 3 each, given a feed containing 0.50 per cent of pure cholesterol and 5 per cent peanut oil, and sacrificed at the end of 90 days. In all the controls, the usual microscopic findings in arteriosclerosis were noted: hyalinization, lipoid infiltration of the subendothelium and media of the aorta, thickening of the intima, hypertrophy of the media, atheromatous plaques, with or without ulceration, and calcified nodules. Lipotropic agents did not prevent aortic lipoidosis or experimental atherosclerosis. With inositol the effect was nil, almost nil with acetyl inositol-betaine, partial with inositol-choline, significant with acetyl inositol alone or combined with choline.

Two of the lipotropic agents used were new products, never before employed to the authors' knowledge: acetyl inositol and dibromocholine disulfide.

All the agents used, with the exception of betaine, assured the protection of the liver against steatosis. Larger doses produced slightly poorer results, and the combinations were not much more active than the single products.

The authors stress that no formal conclusions can be drawn from the results of these limited animal studies, pointing out that an agent effective against steatosis arising from a specific cause may have no effect on steatosis of different origin.—C.-J. Howell

The following studies deal with the metabolism of cholesterol and emphasize the rapidity with which this substance is produced and utilized by the body.

Studies on the Metabolism of Cholesterol in Normal Man and in the Nephrotic Syndrome. I. M. London, G. F. Sabella, and M. M. Yamasaki. *J. Clin. Investig.* 30: 657, 1951.

By studying the rate of incorporation of deuterium into cholesterol in man, the authors found that it takes about 8 days for half the serum cholesterol molecules present in the circulation to be formed. This represents a mean survival time of about 12 days.—S. O. Waife

Rate of Appearance of Dietary Cholesterol in Blood. I. Warner. *Fed. Proc.* 11: 306, 1952.

Small doses of C^{14}-labeled cholesterol were fed to animals and human subjects. The dose in man averaged 2.2 mg./kilo body weight, and was administered in vegetable oil with added phospholipids. The maximal radioactivity was reached in about 2 days. Free cholesterol had a higher specific activity during the first 3 days than esterified cholesterol.—S. O. Waife

The effect of other substances on serum cholesterol is obviously important, since the body can form endogenous cholesterol from acetate and other simple carbon-containing compounds. The significance of total fat and of choline in the diet forms the nucleus of the following papers.

An Experimental Study of Practical Diets to Reduce the Human Serum Cholesterol. E. A. Hildreth, S. M. Mellinkoff, G. W. Blair, and D. M. Hildreth. *J. Clin. Investig.* 30: 649, 1951.

Three of the authors placed themselves on special restricted diets for periods up to one year. The protein and caloric content of their diets was constant throughout. Frequent serum cholesterol determinations were performed while the subject restricted both fat and cholesterol, and later when only cholesterol was restricted, but with normal total fat.

A significant fall in serum cholesterol levels occurred only when total fats were restricted. Adding vegetable fat without cholesterol led to a rise in serum cholesterol to normal levels. Restriction of total fat seemed more decisive than restriction of cholesterol.—S. O. Waife

It will be noticed that the value of the low fat diet was questioned in a previous abstract.

Effects on Liver Lipids and Serum Cholesterol of Various Intakes of Cholesterol and Choline. J. H. Ridout, C. C. Lucas, J. M. Patterson, and C. H. Best. *Fed. Proc.* 11: 274, 1952.

Rats were fed diets containing 4 different levels of cholesterol. Supplementary choline chloride was given to some animals on an otherwise adequate diet. In the absence of choline, only a moderate increase in serum cholesterol occurred on cholesterol ingestion. The presence of choline led to large increases in serum levels.—S. O. Waife

In the emphasis on arterial deposition of cholesterol, the ubiquitous distribution of this substance is frequently overlooked.

Distribution of Exogenous Cholesterol in Tissues of Rat. R. B. Alfin-Slater and L. I. Rice. *Fed. Proc.* 11: 180, 1952.

Feeding deuterium-labeled cholesterol to rats, it

was found that there was a significant increase in cholesterol in the liver, adrenal, and intestine. The spleens were somewhat enlarged, with a normal concentration but greater total cholesterol content. The deuterium concentration was highest in fecal cholesterol, and, in decreasing order, in liver, lung, spleen, adrenal erythrocytes, plasma, intestine, and kidney. The deuterium concentration in body fluids was negligible.—S. O. WAIFE

THE FUNCTION OF VITAMIN B_{12}

The proper clinical use of vitamin B_{12} requires the physician to be aware of the current knowledge of the metabolic effects of this most potent of nutrients. Recent studies have begun to clarify the mode of action of this substance.

Research on the Chemistry of Vitamin B_{12}. K. Folkers, *Intern. Zeit. f. Vitaminforsch.* 23: 429, 1952.

This is a brief review of the chemical analyses of liver extracts leading to the isolation and identification of vitamin B_{12}. This substance is a comparatively large molecule with a composition described by the formula: $C_{61-64}H_{88-92}N_{14}O_{15}PCo$. Various modifications of chemical structures have led to the identification of vitamin B_{12a}, B_{12b}, etc. To avoid confusion the name *cobalamin* was selected to designate all of the vitamin B_{12} molecule except the cyano group. Vitamin B_{12} becomes *cyanocobalimin*, vitamin B_{12a} *hydrozocobalamin*, etc. Evidence for one or more pyrrol-like nuclei in the molecule has also been obtained.—S. O. WAIFE

Metabolic Role of Vitamin B_{12}. C. T. Ling and B. F. Chow. *Fed. Proc.* 11: 249, 1952.

Administration of vitamin B_{12} to patients with pernicious anemia and B_{12}-deficient rats resulted in a marked increase in sulfhydryl (SH) content of red blood cells, primarily due to glutathione, and in blood phospholipids. A high carbohydrate, low iron diet, in addition to glucose injections, reversed these changes, conceivably because of an increased utilization or requirement of B_{12}. The finding that B_{12}-deficient rats had smaller carbohydrate reserves and utilized poorly intravenous glucose further supports the hypothesis that the requirement of vitamin B_{12} is related to carbohydrate intake.—S. O. WAIFE

An important aid to experimental nutrition has been the ability of chemists to label compounds with radioactive elements. As the following paper shows, we can now trace the distribution of vitamin B_{12}.

The Distribution of Radioactivity in the Organs of the Fetus or of Young Rats Born by Mothers Injected with Vitamin B_{12} Containing Co^{60}. B. F. Chow, L. Barrows, and C. T. Ling. *Arch. Biochem. & Biophys.* 34: 151, 1951.

It was possible to follow the pathway of the distribution of vitamin B_{12} by administering the vitamin labeled with radioactive cobalt (Co^{60}) to pregnant rats. Small amounts of radioactivity were detected in the liver and kidneys of mother rats. Much larger amounts were found in the carcasses of newborn rats. As much as 18 per cent of the administered radioactivity was found in all the fetuses and placentas, but no activity was detected in the amniotic fluid.

This provides evidence that vitamin B_{12} is transmitted from mother to progeny through the placenta, and confirms the general, though not definitely proved, impression that water-soluble vitamins are transferred across the placental barrier.—S. O. WAIFE

The maturation of erythrocytes is not only one of the most important effects of vitamin B_{12}, it also has the faculty of being a quantitatively measurable change. This permits an unusual type of experimental observation.

Observations on the Effects of Vitamin B_{12}, Liver Extracts, Folic Acid and Thymine on the Maturation of Megaloblasts in Culture. R. B. Thompson. *Blood* 7: 522, 1952.

Utilizing the technique of human bone marrow culture in serum bottles with human plasma serving as the medium, folic acid was found to exert a maturing effect on megaloblasts of pernicious anemia, while vitamin B_{12}, liver extract, and thymine were impotent. In addition, normal plasma alone produced maturation in one experiment while 40 per cent beef plasma and pernicious anemia plasma were ineffectual and the latter served as the control. It was suggested in one experiment wherein 1 mg. of folic acid in pernicious anemia plasma was not active that an inhibitor to maturation may be present in the plasma of patients with pernicious anemia. Maturation is established by demonstrating a fall in the percentage of immature red cells (megaloblasts and early erythroblasts) which is greater than twice the standard error.

It should be pointed out that the author does not prove maturation. Absolute total counts are not recorded, nor are the percentages of mature forms given. The results might be interpreted as showing that the megaloblasts disappear or disintegrate more rapidly in folic acid than in vitamin B_{12}. Thus the evidence of maturation must be considered presumptive.

This work confirms previous reports from England that folic acid exerts a direct maturing effect upon the megaloblasts of pernicious anemia in vitro while vitamin B_{12} does not. This is in direct opposition to the reported effectiveness of vitamin B_{12} in producing local maturation when instilled directly into the bone marrow of the iliac crest of patients with pernicious anemia and the inability of folic acid to do likewise. This apparent dichotomy is recognized by the author as perhaps an artefact due to the abnormal environment of a serum bottle. However it is now generally recognized that biologically active B_{12} is bound by

some protein and perhaps an insufficient amount of this protein is available in the artificial environment, whereas adequate amounts would be present in the marrow cavity of the ileum. Furthermore, folic acid which presumably is not bound, but must be metabolized to a more active substance, may be "washed away" by the blood in the bone marrow cavity before it has an opportunity to exert an effect, whereas in the culture bottle sufficient time is available for this process to occur. With this type of reasoning it may be possible to harmonize these divergent views as more and more becomes known concerning these two hematinic vitamins.—J. F. MUELLER

The metabolism of a substance is traditionally studied by means of absorption and excretion measurements. Although oral *vitamin B_{12} is described elsewhere (pages 82–84), the following studies will help clarify the problem of dosage.*

Urinary Excretion of Vitamin B_{12}. M. F. Sokoloff, E. H. Sanneman, Jr., and M. F. Beard. *Blood* 7: 243, 1952.

Under normal conditions vitamin B_{12} is absorbed from the gastroenteric tract when intrinsic factor is present. Absorption is slight in the absence of intrinsic factor. Many different proteins (including intrinsic factor) and microorganisms have the property of binding vitamin B_{12}, in which condition it is unavailable for microbiologic assay. There is some evidence that intrinsic factor releases it from conjugation with other proteins.

Very little vitamin B_{12} is excreted in the urine under normal conditions. Large doses must be given parenterally before an appreciable amount appears in the urine. The authors of this paper have reported on the urinary excretion pattern of vitamin B_{12} in six patients with pernicious anemia in remission and six nonpernicious anemia patients.

The doses administered parenterally were 42.2, 63.3, 84.4, and 211.0 micrograms on four successive days; some patients received increasing dosage, others decreasing dosage. The amounts excreted were determined at the end of 2, 5, 8, 11, and 18 hours using *Lactobacillus leichmanii* A.T.C.C. No. 4797, as test organism. Patterns of excretion were similar in the patients with pernicious anemia. With increasing dosage, the amount excreted ranged from 5 to 63 per cent. With decreasing dosage, the excretion ranged from 63 to 12 per cent. Excretion following the 42.2 microgram dose was considerable when the patient had been "saturated" by prior administration of larger doses of vitamin B_{12}. The authors postulate that the large doses of vitamin B_{12} exceed the vitamin B_{12} binding capacity of the plasma and lead to the excretion of free vitamin B_{12} in the urine.—R. W. VILTER

Urinary Elimination of Vitamin B_{12} after Intramuscular Injection in Man. R. Wolff, R. Karlin, P. Drouet, and G. Raubert. *Compt. rend. Soc. de biol.* 145: 989, 1951

After intramuscular injection of therapeutic doses of vitamin B_{12} the urinary excretion of the vitamin was microbiologically determined (with *Lactobacillus leichmannii* No. 4797), after the absence of all factors inhibiting microbe growth or stimulating the effect of vitamin B_{12} had been carefully verified.

The 16 subjects comprised patients with various diseases, including 4 with pernicious anemia. Most received a single intramuscular injection of 50 μg. of vitamin B_{12}. Three of those with pernicious anemia were under treatment and had received 30–50 μg. of vitamin B_{12} per day (a total of 300–500 μg.). The urines were collected before the experiment and for 24 and 48 hours after the injection. With several subjects, the test was repeated 10–20 days later. No vitamin B_{12} was detected in the urine before injection.

Subjects receiving 50 μg. of the vitamin eliminated only part of it, with striking individual variations in the amount. In 7 subjects the total elimination of vitamin B_{12} was less than one μg.; in 6 it reached 20–50 per cent of the amount injected. The maximum appeared during the first 24 hours; between the 24th and 48th hour the urinary vitamin level was nil or very slight, except in a single case, where it reached 5.4 μg. In the same individual there was marked variation in the rhythm of elimination in the 2 successive tests.

The subjects with pernicious anemia appeared to excrete less vitamin B_{12} than the non-anemic subjects.

These studies indicate the low tolerance of the organism for exogenous vitamin B_{12}. Assuming that the average content of the liver in vitamin B_{12} is 0.5 μg. per gram of fresh tissue, one reaches the conclusion that with a dose of the vitamin scarcely equal to 7 per cent of the hepatic reserve, the organism's threshold of assimilation is reached and quickly passed. This low tolerance and its individual variations explain the uncertainties which exist with regard to therapeutical dosages of vitamin B_{12}.—C-J. HOWELL

Observations on the Absorption, Utilization and Excretion of Vitamin B_{12}. C. L. Conley, J. R. Krevans, B. F. Chow, C. Barrows, and C. A. Lang. *J. Lab. & Clin. Med.* 38: 84, 1951.

Vitamin B_{12} was administered orally, intramuscularly, or intravenously to normal subjects and patients with pernicious anemia. The rate of urinary excretion and, in some cases, the concentration of vitamin B_{12} in the plasma were measured.

In 2 of the cases described, there was striking hematological and neurological improvement following parenteral administration of only 25 μg. of vitamin B_{12}. The oral administration of a single dose of 5000 μg. of the vitamin (without gastric juice or other factors) caused a complete hematologic response in a patient with pernicious anemia. Smaller oral doses (1000 and 2000 μg.) induced striking hematological changes, but did not restore blood values to normal. The authors suggest that since complete remission fol-

lowed parenteral administration of 25 μg. of the vitamin, this much or more of the 5000 μg. administered orally must have been absorbed. Thus, to produce the same clinical effect, approximately 200 times as much vitamin B_{12} must be given orally as parenterally.

When more than 25 μg. of vitamin B_{12} was administered parenterally, rapid urinary excretion of the vitamin followed. After injection of 500 μg. or more, urinary excretion was approximately quantitative. Following oral administration of single doses as large as 10,000 μg., there was no measurable increase in urinary excretion of vitamin B_{12} either in normal subjects or in those with pernicious anemia.—C-J. HOWELL

Retention of Crystalline Vitamin B_{12} by Healthy Male Individuals Following Intramuscular Injection. C. Lang, R. A. Harte, C. L. Conley, and B. F. Chow. *J. Nutrition* 46: 215, 1952.

To determine the extent of retention of intramuscularly administered vitamin B_{12} by healthy humans with adequate dietary intakes of the vitamin, single injections of varying amounts of crystalline vitamin B_{12} were given intramuscularly to 16 healthy males, aged 14–45, divided at random into groups of 4, a fifth group serving as controls. Pre- and post-injection urinary output was estimated, the latter in 2 fractions (at 8 and 24 hours). In all cases, independently of the amount of vitamin B_{12} injected, maximum activity in the urine samples appeared during the first 8 hours; an insiginficant amount of activity was found in the fractions representing the following 16 hours.

Urine samples of individuals given 20 μg. of vitamin B_{12} showed an activity of approximately 1 μg., indicating that as much as 19 μg. had been retained. Subjects receiving 30 μg. of the vitamin seemed to have retained up to 29 μg. Those given 50–75 μg. apparently retained as much as 40 and 55 μg. respectively.

It is thus apparent that, just as in the case of stock colony rats, significant amounts of vitamin B_{12} can be retained by healthy, adequately nourished human males when the vitamin is given intramuscularly. The amount retained seems to be proportionate to the amount injected.—C. J. HOWELL

Sequelae to the Administration of Vitamin B_{12} to Humans. B. F. Chow. *J. Nutrition* 43: 323, 1951.

This paper reports observations on the metabolism and fate of orally and parenterally administered vitamin B_{12} and on its effect on nitrogen metabolism in children and on the weight gain of growing children during supplementation of an adequate diet with this vitamin.

Vitamin B_{12} actually could not be found in the urine of normal individuals or untreated pernicious anemia patients following oral administration of as large a dose as 5000 μg. A major portion of the vitamin appeared in the feces. In both types of subjects striking increase in vitamin B_{12} activity in the urine was observed following intramuscular or intravenous injection of 50 to 1000 μg. The results indicate poor absorption of this vitamin in the gastrointestinal tract even in healthy individuals.

In growing children it was found that even after six months on B_{12}-supplemented diets on a daily oral dose of 25 μg. practically no detectable vitamin B_{12} activity was found in the urine. Determinations of vitamin B_{12} in plasma and blood failed to yield evidence of penetration into or adsorption onto the erythrocytes within 15 minutes *in vivo*. Dr. Chow offers several possible explanations for the poor absorption of vitamin B_{12} when given orally. B_{12} activity in foodstuffs may reside in unknown complexes of the vitamin which are absorbable by most people, or there may be a limit to which material responsible for B_{12} activity, if it is not pure B_{12} itself, is absorbed, and this limit may be close to the level at which it is metabolized to yield inactive urinary excretion products. The balance of an oral dose passes through the gastrointestinal tract either unchanged or metabolized or yields only a fraction of the ingested activity in the feces.

When vitamin B_{12} was given parenterally to infants fed on a soybean diet, no increase in nitrogen retention was observed.

Observations were made on the effect of vitamin B_{12} supplementation on the weight gains of 21 chronically ill children, 10 of which suffered from malnutrition, 2 of which had mental and physical defects, 8 with rheumatic heart and congenital heart conditions, and 1 with chronic infection. These results were compared with those obtained on 24 clinically healthy children. The chronically ill children gained greater weight in a given period than the corresponding controls. However, due to the heterogeneity of the subjects with chronic illness and the small numbers of the normal children studied, the results are merely considered suggestive of trends which need confirmation by extended observations and under better controlled conditions.—B. SURE

See Wetzel et al., this issue, page 17, for additional studies on the effect of vitamin B_{12} on children in growth failure.

THE ORAL USE OF VITAMIN B_{12}

The oral use of vitamin B_{12} is of obvious importance. However, certain misconceptions about the efficacy of the oral form of this vitamin still exist. Only recently has it been possible to accurately measure blood and urine levels—a matter of considerable moment in developing our knowledge of this substance, while the gastric defect in patients with pernicious anemia is becoming understandable from the studies with glandular mucoprotein of the stomach. The clinicians, however, should not and do not wait for all the answers to come in, and a number of re-

ports on the therapeutic effectiveness of orally administered vitamin B_{12} are available.

Studies on Vitamin B_{12} in Human Serum. W. G. Unglaub and H. L. Rosenthal. *Proc. Am. Soc. Clin. Investigation.* Atlantic City, May 5, 1952.

A method of assay of serum content of vitamin B_{12} using the microorganism *Lactobacillus leichmannii* has been devised. The average serum concentration of normal fasting subjects was 0.21 millimicrogram per ml. During the day on normal diets the value ranged from 0.11 to 0.42 mμ. per ml. Only slight increases in serum B_{12} were noted after oral administration of high doses by mouth. However, the oral administration of 500 μg. to a patient with pernicious anemia led to a rise in 4 hours of the serum concentration from 0.07 to 0.32 mμ. per ml.

The urinary excretion of vitamin B_{12} was not significantly altered by oral administration of this factor.—S. O. WAIFE

Potentiation of Hematopoietic Effect of Orally Administered Vitamin B_{12} by Glandular Mucoprotein of the Human Stomach. G. B. J. Glass, L. J. Boyd, and C. S. Svigals. *Fed. Proc.* 11: 54, 1952.

It has been demonstrated previously that one of the components of gastric dissolved mucin, glandular mucoprotein from the fundal glands of human stomachs, resembles Castle's intrinsic factor in many properties. This substance is found consistently absent or present only in traces in the gastric juice of patients with pernicious anemia.

In 7 patients with pernicious anemia, daily oral doses of 10 to 30 μg. B_{12} were ineffective. When 50 to 200 mg. of the gastric mucoprotein was added a full hematologic response occurred. In patients with nutritional macrocytic anemia, and who had the mucoprotein in their gastric juices, daily oral administration of 10 to 30 μg. B_{12} led to the return of a normal blood picture.

It appears that the presence of glandular mucoprotein in gastric juice is required for the effectiveness of small doses of vitamin B_{12} by mouth. The quantitative estimation of glandular mucoprotein may be helpful in determining the types of macrocytic anemia which may be expected to respond to oral vitamin B_{12}.—S. O. WAIFE

The clinical aspects of the interrelationships between vitamin B_{12} and folic acid, both being involved in nucleoprotein synthesis and erythropoiesis, are discussed in the observations made on patients with tropical sprue.

The Oral Administration of Vitamin B_{12} in Tropical Sprue. F. Diez-Rivas, R. M. Suarez, F. Hernandez-Morales, and E. P. Santiago. *Ann. Int. Med.* 36: 583, 1952.

Vitamin B_{12} given orally to patients with tropical sprue in single doses of 15 to 50 micrograms induced minor reticulocyte responses and negligible erythrocyte rises. When larger single doses of vitamin B_{12} were given orally (90–450 micrograms) the hematologic responses were no better. Suboptimal responses were obtained when multiple doses of 100 to 400 micrograms were given orally. Six to twelve weeks of repeated therapy were required to increase the erythrocyte and hemoglobin levels and induce a remission in diarrhea and glossitis. When doses of 30 to 60 micrograms of vitamin B_{12} were given together with 75–150 cc. of normal gastric juice daily, the hematologic responses were little better. When the vitamin was given intramuscularly in doses of 15–50 micrograms a day, the hematologic responses were somewhat better but still not maximal and mean corpuscular volumes increased rather than decreased. Folic acid either orally or parenterally in doses of 10–15 milligrams daily induced optimal responses.

It is interesting to compare these results with those obtained in patients with pernicious anemia. In the latter disease one microgram of vitamin B_{12} parenterally per day will usually induce a maximum reticulocytosis and erythrocyte increase. Five to twenty-five micrograms orally per day will not induce a response but when 5 micrograms are combined with 75–150 cc. normal gastric juice, a maximal hematologic response is usually attained. These differences in the responsiveness of sprue and pernicious anemia to vitamin B_{12} with or without gastric juice support the theory that sprue begins as a deficiency of folic acid and to a lesser extent of vitamin B_{12}. These food deficiencies impair the absorptive power of the gastroenteric tract, possibly cause an alteration in enteric microorganisms, and reduce the production of intrinsic factor. Folic acid is complete replacement therapy; vitamin B_{12} is partially effective because there is an element of deficiency of this vitamin in sprue and perhaps because vitamin B_{12} may affect folic acid metabolism directly. On the other hand, in pernicious anemia the primary deficiency is in vitamin B_{12} because lack of intrinsic factor greatly impairs the absorption of this vitamin from the enteric tract. Any deficiency in folic acid that may occur is of a secondary nature. The maximum hematopoietic response is to parenteral vitamin B_{12}, though restoring intrinsic factor together with vitamin B_{12} to the intestine will give a satisfactory response.—R. W. VILTER

The Oral Use of Combined Vitamins B_{12} and Folic Acid in Tropical Sprue. F. Diez-Rivas, F. Hernandez-Morales, and L. M. Meyer. *Ann. Int. Med.* 36: 1076, 1952.

The simultaneous oral administration of suboptimal doses of folic acid (1.67 mg.) and vitamin B_{12} (25 u.) produced what the authors considered optimal hematologic and clinical remissions in five patients with sprue. Three of the five cases were shown to be refractive to folic acid therapy even in the usually effective dose of 10 and 15 mg. daily. None of the cases were given antecedent trials with vitamin B_{12}

by mouth in the dosage employed in the experiment, although previous work had shown this dose (25 u.) to be ineffective. The authors conclude from these experiments that folic acid and vitamin B_{12} act synergistically in megaloblastic anemias and suggest "the possibility that folic acid is needed for the proper absorption and utilization of vitamin B_{12} by the human organism."

These investigations attempted again to demonstrate the interrelationship between folic acid and vitamin B_{12}. The use of suboptimal dosages in combination is notoriously difficult because the old problem of synergism versus additive effect exists and cannot adequately be dispelled. Furthermore it is dangerous to assume that all patients with the same disease will react the same way to a given medication. Thus a demonstration that each of the five patients was refractive to both folic acid (1.67 mg.) and vitamin B_{12} (25 u.) would have been desirable. The fact that two of the patients did not respond to 10 and 15 mg. of folic acid orally, respectively, suggests that these patients might have had a true deficiency of vitamin B_{12}.

It would appear at this time that folic acid and vitamin B_{12} are definitely related in their actions upon erythropoiesis but the exact nature of this interrelationship remains obscure. Although one (folic acid) may have a direct effect on the metabolism of the other (B_{12}) as the authors here have intimated, it may just as well be that they effect the same biochemical reaction at different enzyme levels.—J. F. MUELLER

THERAPEUTIC VALUE OF VITAMIN B_{12}

The value of cyanocobalamin (vitamin B_{12}) in Addisonian pernicious anemia has been established without doubt. Additional reports on its effectiveness (occasionally only moderate) in other types of megaloblastic anemia continue to appear. It behooves the clinician to be aware of the experience of others.

Vitamin B_{12} and Pteroylglutamic Acid in the Treatment of Megaloblastic Anemias. H. O. Niewig, F. S. P. van Buchem, and W. F. Stenfert Kroese. *Acta med. Scandin.* 142: 45, 1952.

The megaloblastic anemias are described as being produced by a deficiency of either vitamin B_{12} or pteroylglutamic acid (PGA). It is of primary importance to know in which category a specific patient belongs because vitamin B_{12} has been shown to have little effect upon those whose anemia is due to PGA deficiency and who show no involvement of the nervous system; contrariwise, those who lack vitamin B_{12} and manifest nervous system lesions are not benefited by PGA. These findings are based on a study of 16 cases of pernicious anemia, 2 cases of steatorrhea, 2 cases of tropical sprue, 3 post-gastrectomy cases, and 3 cases of megaloblastic anemia of pregnancy.

The authors indicate that the bone marrow, the gastrointestinal tract, and the nervous system are all areas characterized by rapid regeneration in which the manifestations of pernicious anemia appear. The neurological lesions are related to a disturbance of ribose nucleic acid synthesis. PGA administration in pernicious anemia is of benefit only insofar as it affects desoxyribose nucleic acid metabolism. It does not influence the abnormalities present in ribose nucleic acid synthesis. Vitamin B_{12} apparently corrects the altered metabolism of both desoxyribose and ribose nucleic acids.—C. R. SHUMAN

Vitamin B_{12} in Megaloblastic Anemia of Pregnancy and Tropical Nutritional Anemia. S. Chaudhuri. *Brit. Med. J.* 2: 825, 1952.

In the treatment of 16 cases of megaloblastic anemia of pregnancy and the puerperium, vitamin B_{12}, parenterally administered, produced a satisfactory hematological response. One patient received iron therapy in addition to B_{12} because of hypochromia. Five patients with tropical megaloblastic anemia were treated with vitamin B_{12}. Four of these had an excellent response, and one responded better to subsequent folic acid therapy. In all cases, the plasma proteins were low initially and showed some increase during the period of observation. Higher than average doses of vitamin B_{12} were necessary in the treatment of these anemias; four micrograms a day was used for mild cases and ten micrograms a day for severe ones.—C. R. SHUMAN

Side-Effects of a Preparation of Vitamin B_{12}. P. D. Bedford. *Brit. Med. J.* 1: 690, 1952.

Side-effects of local pain at the site of injection of vitamin B_{12} with associated fever, chills, and malaise are described. These reactions occurred only with the B_{12} concentrate prepared from *Streptomyces griseus* and were not obtained with the preparation derived from liver extract or from the B_{12} which was purified by crystallization from the mould. Skin tests performed on 100 people showed 14 to be sensitive to vitamin B_{12} concentrate, of which six suffered side-effects following injection. The cutaneous reactions and side-effects were twice as common among people who had previously received antibiotics. It is likely that impurities from the mould fermentation liquor are responsible for the sensitivity reaction. Possibly sensitization of these impurities in a preparation of B_{12} may sensitize patients to certain antibiotics.—C. R. SHUMAN

Reviews of Recent Books

Nutrition and Diet Therapy (tenth edition) by F. T. Proudfit and C. H. Robinson, Macmillan Co., New York, 1950, pp. 950, $4.50.

The tenth edition of this text has been revised so that it may readily be used with the *New Manual for Teaching Dietetics to Student Nurses* prepared by the American Dietetic Association. However, in the section which deals with the subject of normal nutrition, some of the details given are beyond the grasp of the student nurse due to her limited background in organic and biochemistry. An example of this is the discussion of the functions of the B-complex vitamins on pages 120 and 121 where the role of these vitamins in oxidative enzyme systems is described. Since the authors do present this book as a useful reference for college students of dietetics, the nutritionist in public health, the dietitian and the physician, perhaps they are justified in including these detailed discussions. In the teaching of student nurses, parts of the text must be simplified or even omitted in some instances.

It is gratifying to find a clear-cut explanation of the calculation of the diabetic diet according to the method which has been approved by the American Dietetic Association, the American Diabetes Association, and the U. S. Public Health Service—Diabetes Branch. Supplementary information concerning food exchange lists is found in the appendix.

Emphasis is constantly placed on the importance of using a normal diet as the basis for therapeutic diets. The listing in parallel columns of *foods allowed* and *foods to avoid* under specific conditions makes the dietary outlines much more useful.

Excellent material is included on food selection, preparation, and meal service for the patient and the family. This is valuable background information which aids the student nurse in applying her knowledge of food values in the hospital and in her future home. Small quantity recipes are clearly and accurately presented. K.E.L.

Methods of Vitamin Assay (second edition), prepared and edited by the Association of Vitamin Chemists, Inc., Interscience Publishers, New York and London, 1951, pp. 301, $5.50.

The Association of Vitamin Chemists, in sponsoring a second edition of this useful work, has continued the plan originally followed by making separate committees of experts responsible for each of the phases of vitamin methodology discussed. Only those methods are presented that have been successfully applied to the assay of a variety of materials. The advice of numerous consultants and reviewers was obtained, including some of the foremost workers in the field. The result is an authoritative presentation of methods, each in a separate chapter, for vitamins A, carotene, ascorbic acid, thiamine, riboflavin, niacin, pantothenic acid, vitamin B_6, folic acid, biotin, and vitamin B_{12}. Methods for the last six are included for the first time in this edition. The material dealing with the others has been revised and brought up to date. Methods for other vitamins are discussed in less detail, but sufficient information is given to enable the prospective user to choose between the methods available. Chapters on sampling for vitamin analysis and on microbiological assay techniques continue to be valuable sources of information. The former includes a discussion of the statistics of sampling.

The main purpose of this book is to provide a manual for the analyst with directions for carrying out assays. These directions are given in full detail, step by step, with comments and annotations. For methods as complex as those used for assay of vitamins, minor differences in technique may influence substantially the results of a procedure, and the emphasis on detail is fully justified.

Alternative methods are listed, and where several methods exist, based on different principles, each is described.

The discussion of techniques is preceded in each chapter by a brief review of the history, chemical characteristics, various forms and functions of the vitamin. The specificity and major sources of error of the methods are evaluated. The plan of the volume prevents its being an up-to-the-minute source of information, and although there are a few 1950 references, most are dated 1948 and earlier. However, as a manual for laboratory workers in the field of vitamins, it is an indispensible tool. J.G.R.

The Vitamin B Complex by F. A. Robinson, M.Sc., F.R.I.C., John Wiley & Sons, New York, 1951, pp. 688, $9.00.

The author of this book has performed a great service to workers in the nutrition field. The tremendous volume of published material on members of the vitamin B complex group is organized and summarized in convenient sections. For each member of the B family all important and recent findings relative to isolation, estimation, occurrence, analogous functions, and effects on microorganisms, plants, animals, and man are presented.

There are numerous references and a convenient subject and author index. The wide coverage of the pertinent literature can be judged by the fact that there are 45 references to a 5-page subsection on the microbiological production of riboflavin, and 48 references on the effect of biotin deficiency in animals.

As the author states in the preface, it is impossible to cover *all* aspects of the vitamin B group in complete detail, enough to satisfy clinicians, chemists, agriculturists, and physiologists. Thus the purely medical aspects are described in less detail than the biologic or pharmacologic aspects. Nevertheless, as a source book, a convenient reference and starting point in a literature survey, and as an attempt at integration of widely scattered data, this book can be heartily recommended. S.O.W.

Industrial Nutrition by Magnus Pyke, Macdonald and Evans, London, 1950, VII, pp. 205, 10 s.

The industrial worker shares with the other members of the species *Homo sapiens* many of the needs of the mythical but useful creation, the average adult man (and woman). What is so special about the man in industry that scientific bodies create Committees on the Nutrition of Industrial Workers* and authors publish articles and whole books† on this topic?

Well, several things. His caloric needs vary over a considerable range and their knowledge must form a basis for differential rationing in times of prolonged shortage of food. He is exposed to hot and cold working environments, and these affect some of his nutrient requirements. In several occupations, a contact with toxic compounds is unavoidable; there is limited evidence, based primarily on animal experimentation, that nutritional factors may increase the resistance to some toxic substances. Culinary rather than nutritional problems arise from working on different shifts, including the night shift. There is a problem of the optimal frequency and spacing of meals. Tenacious local dietary habits may foster or endanger adequate nutrition.

Most forms of malnutrition affecting the industrial worker will result in a fall of production efficiency. This is perhaps the most important single fact which has directed attention to the nutrition of the worker in industry. Thus, the provision of canteens during the First and, at a much accelerated rate, during the Second World War was dictated not by a newly gained nutritional insight but by the need to assure top production. The historically minded nutritionist may wish to look up Noel Curtis-Bennett's *The Food of the People: Being the History of Industrial Feeding* (Faber and Faber, London, 1949) devoting considerable space to the development of industrial canteens. International Labor Office (*Nutrition in Industry,* Montreal, Canada, 1946) has presented the picture of wartime feeding of industrial workers in Canada, the United States, and Great Britain, with emphasis on industrial feeding management. But for a discussion of the nutritional principles on which a sound program of feeding industrial workers should be based, the reader must turn to the small, yet meaty, volume by Dr. Pyke.

The author has considered the problems of industrial nutrition within a larger framework of the scientific study of human nutrition, and although he makes an occasional excursion into dietetics, e.g., in discussing food wastage and the effects of cooking on the nutritional value of food, the focus of his presentation is on the relationship between the nutrition of industrial workers and their health and efficiency. The industrial physician and the industrial nurse, as well as the practical dietitian and the research worker concerned with human nutrition, will find this readable volume reliable in respect to known facts, and wise in its interpolations and practical recommendations.

JOSEF BROŽEK

Textbook of Biochemistry by E. S. West and W. R. Todd, Macmillan Co., New York, 1951, pp. 134, $12.00.

A close examination of this textbook reveals the extensive development of biological chemistry within recent years and the growing importance of biochemical principles in the practice of medicine. Drs. West and Todd have not only expanded the classical chapters in this field but have also incorporated into this text the fundamentals of chemistry which provide the structure upon which biochemistry is based, the newer developments in biochemistry which lead to a better understanding of cellular chemistry and function, and the principles of biochemistry which relate to medicine and nutrition.

The chapters entitled "Introduction to Intermediary Metabolism," "Organic Phosphates in Metabolism," "Antimetabolic Agents," along with the chapters on metabolism, introduce the readers to the classical and recent methods used in the study of metabolism, the energy requirements for individual biochemical reactions, the role of hormones, vitamins, antimetabolites, and drugs as controlling agents in biochemical reactions, and the significance of metabolic derangements in medicine.

Detailed chapters on body fluids serve to introduce to beginners in the study of medicine the fundamentals related to the maintenance of the internal environment of the cell. This subject, though pioneered by the great Claude Bernard, has only recently been introduced into the biochemical curriculum.

* Food and Nutrition Board, National Research Council.

† R. S. Goodhart and M. E. Shils in *Clinical Nutrition,* Hoeber, New York, 1950, pp. 771, 171 references; E. Simonson, in *Nutrition Fronts in Public Health,* Nutrition Symposium Series No. 3, The National Vitamin Foundation, New York, 1951, pp. 72, 71 references.

Finally, this text has also emphasized the nutritional aspects of biochemistry. The chapters on nutrition and foods introduce the subject of nutrition to the medical curriculum. The authors should be congratulated on their efforts to introduce the subject early in the medical curriculum so that the student will realize the importance of nutrition later in his clinical studies and in clinical practice.

The authors are also to be complimented for their extensive use of charts and tables to illustrate the text and for their extensive bibliography. C.A.

Current Therapy 1952, edited by H. F. Conn, M.D., W. B. Saunders Co., Philadelphia, pp. 849, $11.00.

This book of management of diseases occurring in medical practice is a summation of the work of some 275 contributors. It is developed under the able leadership of Dr. Howard F. Conn and twelve consultants. The consultants as well as the contributors are recognized medical teachers and authors, who have shown a special interest in the specific disease discussed. The book is arranged in 16 sections. Fifteen sections deal with definitive plans of therapy of specific diseases covered in the particular section, for example, Infectious Diseases, Diseases of the Cardiovascular, Respiratory, Digestive Systems, etc. Section 16 includes a roster of drugs, a table of metric and apothecary systems, and a table for making percentage solutions. The preceding 15 sections provide information on present-day methods of managing illness which in various authors' experience are of proved value. The individual discussions are brisk and detailed, and presented in a clear, concise fashion. This should prove particularly useful to the busy practitioner who is unable to keep up with the prodigious development in our knowledge of disease, synthesis of drugs, and changes in therapeutic modalities.

Since treating an individual afflicted with a disease requires knowing the "total" patient, and understanding the underlying physiologic and biochemical disturbances, as well as the morphologic background produced by the disease, it would have been desirable to have had a brief, to-the-point discussion of the background upon which a specific therapeutic plan is based. Limitation of space probably accounts for insufficient emphasis on this phase of the discussion. It is this reviewer's opinion that this could have been overcome advantageously by deleting the duplication of variant methods detailed by different authors discussing the same specific disease. After all, therapy of a disease has evolved from the experience of many physicians; the peculiar variant method of the original worker could have been presented in a condensed abstract form. The bibliography is very sparse, and in many discussions totally absent. However, this is not a serious defect. In general, the book will be found a very useful addition to the medical library of the practicing physician. The text throughout is printed with a good large type and is set in a easy-to-read two-column format. The omissions noted above do not deter the reviewer from highly recommending it to the general practitioner and medical student. M.G.W.

Diseases in Old Age by R. T. Monroe, Harvard University Press, Cambridge, 1951, pp. xi + 407 $5.00.

As the subtitle indicates, this is "a clinical and pathological study of 7941 individuals over 61 years of age" who entered the medical service of the Peter Bent Brigham Hospital in Boston between 1913 and 1943. Detailed statistics are presented on the incidence of the major diseases grouped in 11 categories and of other diseases occurring simultaneously with a given disease. Thus, malnutrition was recorded in 4 per cent of patients with psychoneurosis, while 27 per cent of the cases of cerebral arteriosclerosis associated with psychosis showed a definite to extreme loss of weight. In the case of cancer of the stomach, loss of weight was present at the time of admission in 83 per cent of the patients. The magnitude of the weight losses was not specified.

Chronic alcoholism, a peculiar form of malnutrition, was present in 4.7 per cent of the men and 0.8 per cent of the women. Malnutrition, in a generally understood sense, was mentioned in 21 per cent of chronic alcoholics.

The characterization of the general nutritional status and the classification of individuals into 5 categories (clearly underweight, approximately normal in weight, moderately, considerably, and extremely overweight) was based on clinical judgment, without reference to objective criteria. For the hospitalized old men, the percentages of individuals in these 5 categories were 31, 43, 17, 7, and 2; for women 20, 47, 21, 9, and 3. The comment is made that "obesity, then, is not a common problem in old age. Nor is it often a serious problem, for most of the obese cases . . . were quite free from cardiovascular, diabetic, and cerebral disorders" (p. 282). This is in striking contrast, at first glance at least, with the experience of the insurance companies, and underlines the need for a clarification of ideas and for further research in this area. Objective evaluation of the degree of obesity and combination of longitudinal with the cross-sectional approach are prerequisites of an effective attack on this problem.

Whereas general malnutrition was relatively frequent, specific diseases due to deficiency of vitamins were diagnosed in very few old people. One case of vitamin A deficiency, 48 of "avitaminosis B" (including beri-beri, sprue, polyneuritis, and a pellagra-like syndrome), 3 of scurvy, and 17 of osteomalacia. These statistics are probably to be trusted less than those on diseases of non-nutritional origin. The author admits that "it is possible that clinical recognition has been dull."

The section on nutritional disorders, forming only a small part of the book, will be found disappointing by the critical reader looking for solidly established facts. However, the difficulty inherent in obtaining the desired facts should not be minimized. The sound clinical judgment permeating the whole volume will be appreciated by the practitioner of geriatrics. With reference to matters nutritional, the author comments: "The geriatrician who is determined to conquer malnutrition must go far off the beaten path of medicine. His prescription is equal parts of good food, good cooking, good health, good people to eat with, good places to eat, good reasons for eating."

JOSEF BROŽEK

Annual Review of Medicine, Vol. 3, 1952, edited by W. C. Cutting, M.D., Annual Reviews, Inc., Stanford, 1952, pp. 442, $6.00.

As with previous issues, this valuable review of current progress in selected spheres of medicine will be of particular usefulness to workers in academic and research fields. Of special interest to our readers is an excellently written review on tropical nutrition and kwashiorkor by J. W. P. Davies of Uganda, East Africa. Over 160 references are quoted and tie together a widely scattered world literature. Other nutritional reports are covered in other chapters. A detailed subject and author index lends practicality to this serviceable volume. S.O.W.

The Master Dictionary of Food and Cookery and Menu Translator by Henry Smith, Philosophical Library, New York, 1951, pp. 263, $4.75.

This book presents an alphabetical listing of cooking processes, dishes, and foods which may be unfamiliar to the average reader. The historical background and the English translation of foreign names are presented. Every gourmet will be interested in the fact that sausages were mentioned in the oldest cookery book known, A.D. 228, or that the Scotch ptarmigan turns white during winter and should be roasted if young or braised if old.

If curious epicurean lore interests one, this book will be useful. S.O.W.

Books received for review by the *Journal of Clinical Nutrition* are acknowledged in this column. As far as practicable, those of special interest are selected, as space permits, for a more extensive review.

Food and Nutrition (second edition) by E. W. H. Cruickshank, Williams & Wilkins Co., Baltimore, 1951, pp. 443, $6.50.

Bridges' Dietetics for the Clinician (fifth edition), edited by H. J. Johnson, Lea & Febiger, Philadelphia, 1949, pp. 898, $12.00.

Diabetes Control by E. L. Bortz, Lea & Febiger, Philadelphia, 1951, pp. 264, $3.50.

Low-Sodium Diet (A Manual for the Patient) by T. B. Rice, Lea & Febiger, Philadelphia, 1951, pp. 103, $2.75.

Nutrition News

☆ *News of activities in the field of clinical nutrition should be submitted to the Editorial Office of the* JOURNAL.

THE REGISTRY OF NUTRITIONAL PATHOLOGY

The Registry of Nutritional Pathology is a new central agency for the accumulation of material in this specific field. This Registry is a unit of the American Registry of Pathology, within the Armed Forces Institute of Pathology, and is under the general supervision of the Committee on Pathology of the National Research Council. The American Institute of Nutrition which initiated the project has the general administrative responsibility and has a Committee to carry out this function.

The Registry has five main functions:

1. Accumulation and maintenance of collections of pathologic materials and related case records in such special fields of nutritional diseases as are not commonly encountered in individual clinics.

2. Provision of consultation service.

3. Preparation of teaching material.

4. Establishment of facilities for the training of students and fellows in the pathology of nutritional diseases.

5. Facilitation of the accessibility of the materials for students and qualified investigators.

Autopsy material and biopsy specimens are solicited. They must be accompanied by a brief clinical history.

Further information is available from Dr. Herbert Pollack, 70 East 77th Street, New York, N. Y., Chairman of the Committee for the Registry of Nutritional Pathology.

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